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TITLE OF THE INVENTION (200 characters max)

NOVEL IDO INHIBITORS AND METHODS OF USE

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☒ No

☐ Yes, the name of the U.S. Government agency contract number is: _____

Respectfully submitted
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PTO Reg. No. 43,047

☐ Additional inventors are being named on separately numbered sheets attached hereto

NOVEL IDO INHIBITORS AND METHODS OF USE

By George C. Prendergast
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William Malachowski

FIELD OF THE INVENTION

This invention relates to the fields of oncology and chemotherapy. Specifically, the invention provides novel compounds and methods for the treatment of cancer.

BACKGROUND OF THE INVENTION

Several publications and patent documents are cited in this application in order to more fully describe the state of the art to which this invention pertains. The disclosure of each of these citations is incorporated by reference herein.

Tumors characteristically express atypical, potentially immunoreactive antigens that are collectively referred to as tumor antigens. Accumulating evidence suggests that the failure of the immune system to mount an effective response against progressively growing tumors is not attributable to a lack of recognizable tumor antigens. Immunosuppression by tumors is poorly understood and mechanisms by which tumors may escape immune surveillance are poorly explored. Recently, it has been shown that cytotoxic T cells become tolerized by a reduction in local concentrations of tryptophan that are elicited by indoleamine 2,3-dioxygenase (IDO) activity.

IDO is an oxidoreductase that catalyzes the rate-limiting step in tryptophan catabolism. This enzyme is structurally distinct from tryptophan dioxygenase (TDO), which is responsible for dietary tryptophan

catabolism in the liver. IDO is an IFN-γ target gene that has been suggested to play a role in immunomodulation (Mellor and Munn (1999) Immunol. Today. 20:469-473). Elevation of IDO activity depletes the levels of tryptophan in local cellular environments. Induction of IDO in antigen-presenting cells, where IDO is regulated by IFN-γ, blocks the activation of T cells, which are especially sensitive to tryptophan depletion. T cells must undergo 1-2 rounds of cell division to become activated, but in response to tryptophan depletion they arrest in G1 instead. In this way, IDO has been proposed to inhibit the T_H1 responses that promote cytotoxic T cell development.

The main evidence for the role of IDO in immunosuppression is demonstrated by the ability of 1-methyl-tryptophan (1MT), a specific and bioactive IDO inhibitor (Cady and Sono (1991) Arch. Biochem. Biophys. 291:326-333), to elicit MHC-restricted and T cell-mediated rejection of allogeneic mouse concepti (Mellor et al. (2001) Nat. Immunol. 2:64-68; Munn et al. (1998) Science. 281: 1191-1193). This effect is consistent with the high levels of IDO expression in placental trophoblast cells (Sedlmayr et al. (2002) Mol. Hum. Reprod. 8:385-391).

Significantly, IDO activity has been shown to be elevated frequently in human tumors and/or in cancer patients (Yasui et al. (1986) Proc. Natl. Acad. Sci. USA. 83:6622-6626; Taylor and Feng (1991) FASEB J. 5:2516-22). Since IDO can modulate immune responses, one logical implication is that IDO elevation in cancer may promote tumor immunosuppression (Mellor and Munn (1999) Immunol. Today. 20:469-473; Munn et al. (1999) J. Exp. Med. 189:1363-1372; Munn et al. (1998) Science. 281:1191-1193). This possibility is supported by the

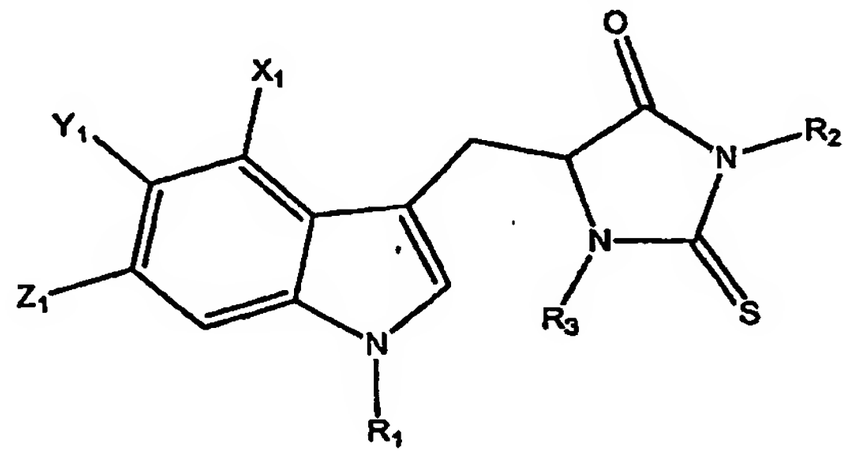
observation that many cancers, including breast cancer, are characterized by a loss of beneficial immune functions that can limit malignant development. For example, T_H1 responses, of which IFN-γ production is a hallmark, that promote the production of cytotoxic T cells are suppressed during cancer progression. A resultant hypothesis of this data was that if IDO drives cancer progression by blunting T cell activation, then IDO inhibition in animals should blunt tumor growth by reversing IDO-mediated immunosuppression. However, delivery of the IDO inhibitor 1-methyl-tryptophan (1MT) only retarded and did not prevent tumor growth in a mouse model (Friberg et al. (2002) Int. J. Cancer 101:151-155; US Patent 6,482,416).

Cellular signal transduction, i.e., the series of events leading from extracellular events to intracellular sequelae, is an aspect of cellular function in both normal and disease states. Numerous proteins that function as signal transducing molecules have been identified, including receptor and non-receptor tyrosine kinases, phosphatases and other molecules with enzymatic or regulatory activities. These molecules generally demonstrate the capacity to associate specifically with other proteins to form a signaling complex that can alter cellular proliferation.

It has been implicated that aberrant signal transduction can lead to malignant transformation, growth, and progression. Accordingly, inhibitors of signal transduction pathways have been used to treat cancer. During the past few years, a number of signal transduction inhibitors (STIs) have been developed and their ability to suppress tumor growth is currently under investigation.

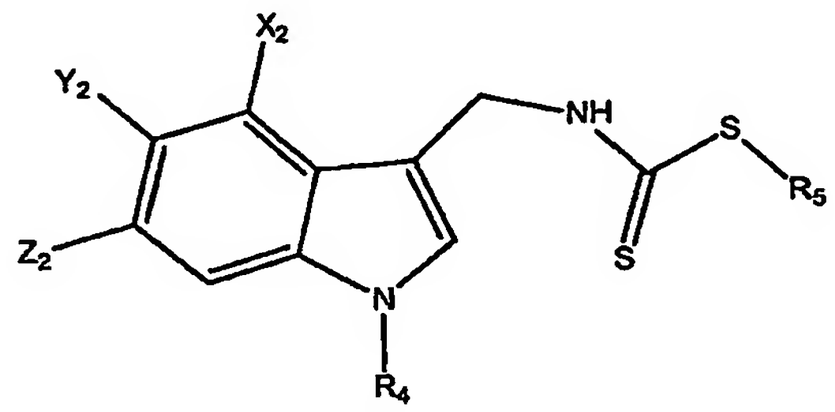
SUMMARY OF THE INVENTION

In accordance with one aspect of the invention, novel inhibitors of indoleamine 2,3-dioxygenase (IDO) activity are provided. The novel compounds have a formula selected from the group consisting of formula (I):



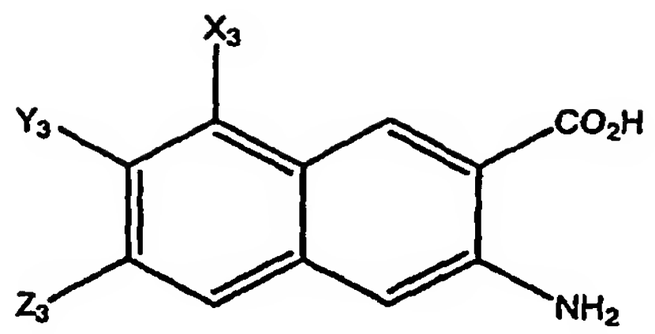
wherein X_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_1 is H or CH_3; R_2 is selected from the group consisting of H, alkyl and aryl; and R_3 is selected from the group consisting of H, alkyl and aryl;

formula (II):



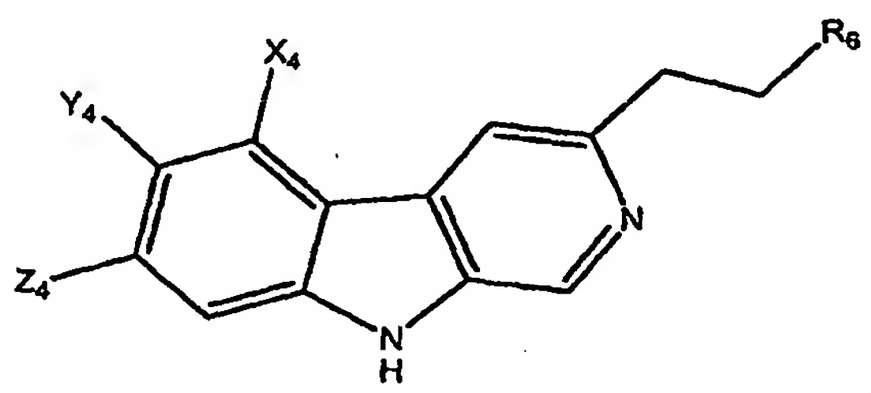
wherein X_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_4 is H or CH_3; and R_5 is selected from the group consisting of H, alkyl and aryl;

formula (III):



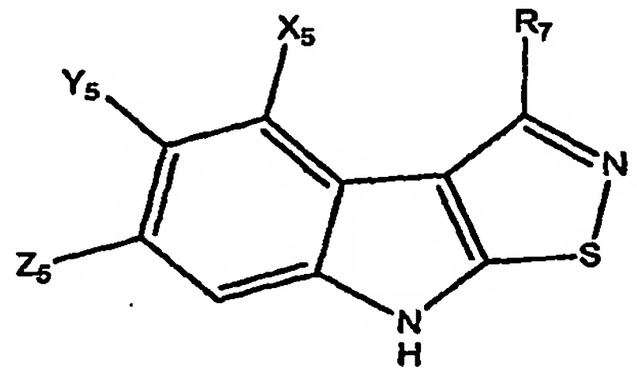
wherein X_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and Z_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl;

formula (IV):



wherein X_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_4 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_6 is alkyl or aryl;

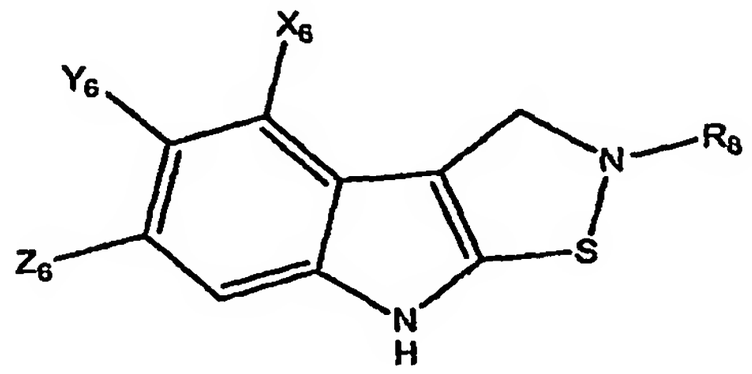
formula (V):



wherein X_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_5 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl,

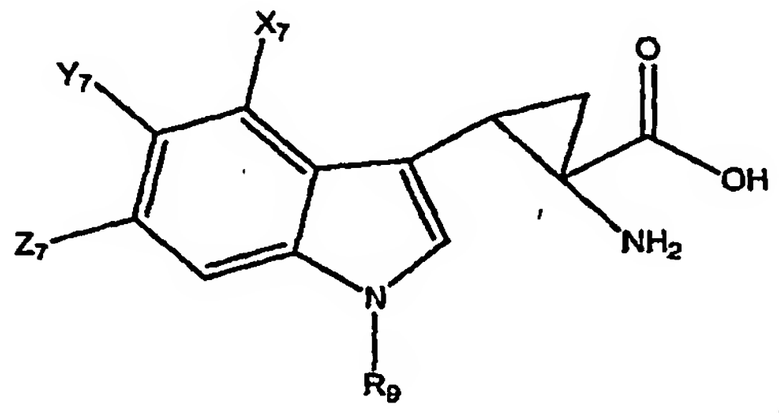
and aryl; Z_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_7 is alkyl or aryl;

formula (VI):



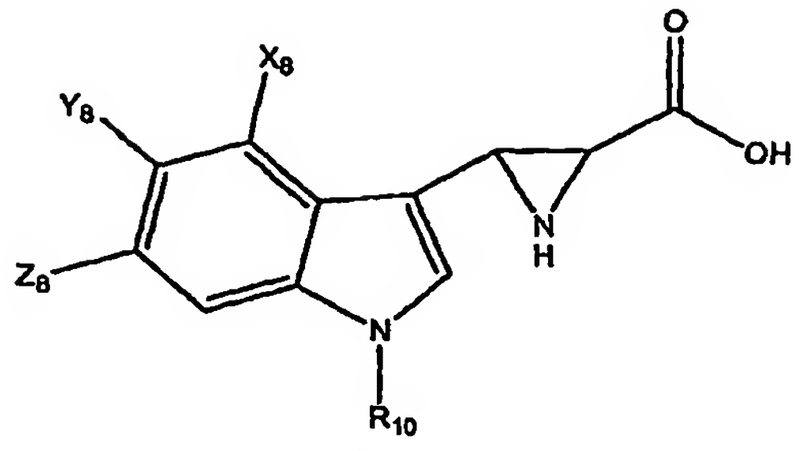
wherein X_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_6 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_8 is alkyl or aryl;

formula (VII):



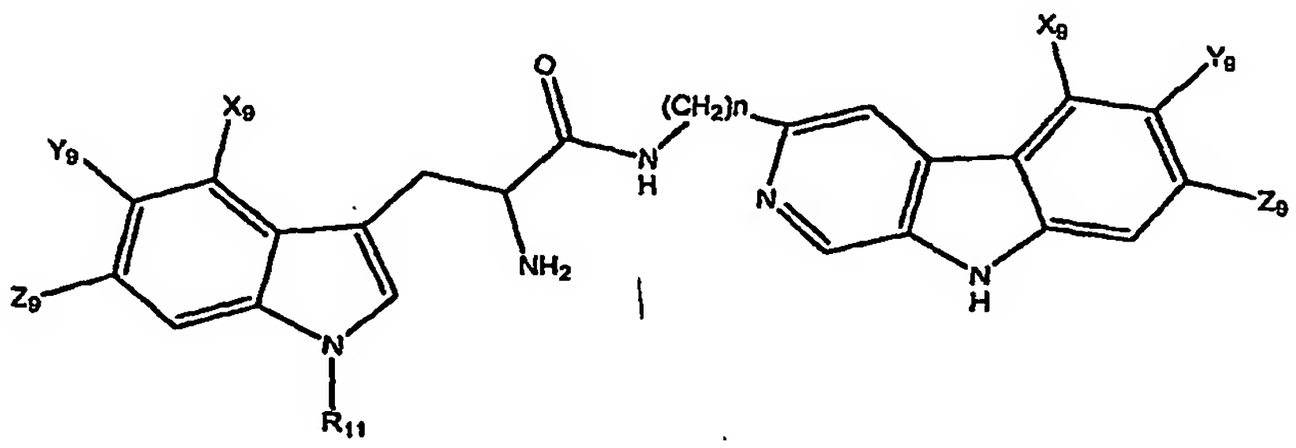
wherein X_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_9 is H or CH_3;

formula (VIII):



wherein X_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{10} is H or CH_3; and

formula (IX):



wherein X_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_9 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{11} is H or CH_3.

According to another aspect of the present invention, a method for treating a cancer in a patient is provided. The method comprises administering an effective amount of a pharmaceutical composition comprising at least one indoleamine 2,3-dioxygenase (IDO) inhibitor, preferably a novel inhibitor of the instant invention, in a pharmaceutically acceptable carrier medium.

In another embodiment of the invention, a method for treating a cancer in a patient in need thereof is

provided. The method comprises administering to the patient, concurrently or sequentially, an effective amount of at least one indoleamine 2,3-dioxygenase (IDO) inhibitor and at least one signal transduction inhibitor (STI). In a particular embodiment of the invention, the at least one STI is selected from the group consisting of bcr/abl kinase inhibitors, epidermal growth factor (EGF) receptor inhibitors, her-2/neu receptor inhibitors, and farnesyl transferase inhibitors (FTIs). The compounds may be administered in a pharmaceutically acceptable carrier medium.

According to yet another aspect of the instant invention, yet another method for treating a cancer in a patient in need thereof is provided. The method comprises administering to the patient, concurrently or sequentially, an effective amount of at least one immunomodulator other than an IDO inhibitor and an effective amount of at least one cytotoxic chemotherapeutic agent or at least one STI. In a particular embodiment the at least one immunomodulator is selected from the group consisting of CD40L, B7, B7RP1, ant-CD40, anti-CD38, anti-ICOS, 4-IBB ligand, dendritic cell cancer vaccine, IL2, IL12, ELC/CCL19, SLC/CCL21, MCP-1, IL-4, IL-18, TNF, IL-15, MDC, IFNa/b, M-CSF, IL-3, GM-CSF, IL-13, and anti-IL-10. In another particular embodiment, the at least one cytotoxic chemotherapeutic agent is selected from the group consisting of placitaxel (Taxol®), cisplatin, docetaxol, carboplatin, vincristine, vinblastine, methotrexate, cyclophosphamide, CPT-11, 5-fluorouracil (5-FU), gemcitabine, estramustine, carmustine, adriamycin (doxorubicin), etoposide, arsenic trioxide, irinotecan, and epothilone derivatives.

In yet another embodiment of the present invention, a method for treating a chronic viral infection in a

patient in need thereof is provided. The method comprises administering to the patient, concurrently or sequentially, an effective amount of at least one indoleamine 2,3-dioxygenase (IDO) inhibitor and at least one chemotherapeutic agent. The at least one chemotherapeutic agent may be selected from the group consisting of placitaxel (Taxol®), cisplatin, docetaxol, carboplatin, vincristine, vinblastine, methotrexate, cyclophosphamide, CPT-11, 5-fluorouracil (5-FU), gemcitabine, estramustine, carmustine, adriamycin (doxorubicin), etoposide, arsenic trioxide, irinotecan, and epothilone derivatives. In a particular embodiment of the invention, the treated chronic viral infection is selected from the group consisting of: hepatitis C virus (HCV), human papilloma virus (HPV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus, coxsackie virus, human immunodeficiency virus (HIV). In another particular embodiment, the compounds may be administered in a pharmaceutically acceptable carrier medium.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides a scheme for synthesizing thiohydantoin derivatives.

Figure 2 provides a scheme for derivatizing indole at C-4 and N-1 positions.

Figure 3 provides a scheme for synthesizing C-6 substituted indoles.

Figure 4 provides a scheme for synthesizing C-4, C-5, and C-6 Trisubstituted indoles.

Figure 5 provides a scheme for an alternative synthesis scheme of thiohydantoin derivatives.

Figure 6 provides a scheme for synthesizing brassinin derivatives.

Figure 7 provides a scheme for synthesizing C-5 and C-6 substituted β-carboline derivatives.

Figure 8 provides a scheme for synthesizing C-3 alkyl substituted β-carboline derivatives.

Figure 9 provides a scheme for an alternative synthesis scheme of β-carboline derivatives.

Figure 10 provides a scheme for synthesizing 3-amino-6/7-bromo-2-naphthoic acid.

Figure 11 provides a scheme for synthesizing C-6, C7, and C-8 trisubstituted 3-amino-2-naphthoic acids.

Figure 12 provides a scheme for an alternative synthesis scheme of C-6, C-7, and C-8 trisubstituted 3-amino-2-naphthoic acids.

Figure 13 provides a scheme for synthesizing brassilexin derivatives, i.e. compounds having the formula of formula (V) or (VI), wherein R_7 or R_8 is H.

Figure 14 provides a scheme for synthesizing brassilexin derivatives, i.e. compounds having the formula of formula (V), wherein R_7 is not H.

Figure 15 provides a scheme for synthesizing brassilexin derivatives, i.e. compounds having the formula of formula (VI), wherein R_8 is not H.

Figure 16 provides a scheme for synthesizing cyclopropyl tryptophan derivatives, compounds having the formula of formula (VII).

Figure 17 provides a scheme for synthesizing aziridinyl tryptophan derivatives, compounds having the formula of formula (VIII).

Figure 18 provides a scheme for synthesizing tethered competitive/noncompetitive derivatives, compounds having the formula of formula (IX).

Figure 19A and 19B are graphs showing the results of an enzyme assay for IDO inhibitors. Global nonlinear regression analysis of enzyme kinetic data obtained for

human IDO in the presence of increasing concentrations of A) 1MT and B) MTH-Trp. Data were plotted and analyzed using the Prism4 software package (GraphPad). Best fit values of Ki for 1MT = 34.6μM and for MTH-Trp = 11.4μM

Figure 20 is a graph showing the result of a cell-based IDO inhibitor assay. Results of 2 log dose escalation studies for 1MT against IDO, 1MT against TDO, and MTH-Trp against IDO. Data were plotted using the Prism4 data analysis program (GraphPad), and Hillslope and EC50 values were determined by nonlinear regression analysis.

Figure 21 is a schematic diagram of the kynurenine metabolism pathway. IDO is an extrahepatic, interferon-γ inducible oxidoreductase. The product of the IDO reaction, *N*-formylkynurenine is rapidly hydrolyzed to kynurenine. Kynurenine is distributed between tissue and blood spaces because there is little or no activity of the enzymes that further metabolize kynurenine in tissues. The major route of kynurenine clearance is excretion in urine after conversion to xanthurenic acid in the liver and/or kidneys, although it is also an intermediate in the biosynthetic pathway that produces nicotinamide adenine dinucleotide (NAD) (Takikawa et al. (1986) J. Biol. Chem. 261:3648-3653; Thomas and Stocker (1999) Redox. Report 4:199-220).

Figures 22A-D are chromatograms showing the results of HPLC analysis of mouse serum. Serum was prepared by incubating collected blood samples at 4°C overnight and removing the clot. Protein was removed by TCA precipitation. Samples were resolved on a 250mm x 4.5mm Luna 5µ C18 column (Phenomenex) in isocratic buffer consisting of 20% MeOH, 5% acetonitrile, 10mM KPO_4 (pH 5.3), 0.15mM EDTA. Serum samples were prepared from male FVB strain mice treated as follows: A) Untreated (serum

was spiked with 30μM each of the following control compounds; tryptophan, kynurenine, and 1MT); B) Untreated (55μM serum tryptophan is detectable); C) LPS challenged for 24 hrs. (induction of kynurenine to 5.6μM is detectable), D) 1MT pellets implanted subcutaneously for 3 days (104μM 1MT is detectable). Output sensitivity (Y-axis) has been adjusted at 6.66 and 14.5 minutes to optimize for each anticipated peak height. Ky = kynurenine, W = tryptophan, 1MT = 1-methyl-tryptophan.

Figure 23 is a graph illustrating the fold change in tumor volume of MMTVneu mice either mock treated (untreated) or treated with 1MT, L-744,832, 1MT and L-744,832. Each data point was determined from an individual mouse and the bars indicate the mean of the data points as listed at the bottom of the graph.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment of the present invention, a group of novel compounds exhibiting IDO inhibitory activity are provided. Also encompassed within the invention are pharmaceutical compositions comprising the same and methods of use thereof for inhibiting tumor growth.

In yet another embodiment of the present invention, a combination treatment protocol comprising administration of an IDO inhibitor with a signal transduction inhibitor (STI) is disclosed, which provides an unexpectedly effective means of suppressing tumor growth.

In still another embodiment of the present invention, a combination treatment protocol, for the treatment of a chronic viral infection, comprising the administration of an IDO inhibitor and a chemotherapeutic agent, is provided.

I. Definitions

The term "IDO inhibitor" refers to an agent capable of inhibiting the activity of indoleamine 2,3-dioxygenase (IDO) and thereby reversing IDO-mediated immunosuppression. An IDO inhibitor may be a competitive, noncompetitive, or irreversible IDO inhibitor. "A competitive IDO inhibitor" is a compound that reversibly inhibits IDO enzyme activity at the catalytic site (for example, without limitation, 1-methyl-tryptophan); "a noncompetitive IDO Inhibitor" is a compound that reversibly inhibits IDO enzyme activity at a non-catalytic site (for example, without limitation, norharman); and "an irreversible IDO inhibitor" is a compound that irreversibly destroys IDO enzyme activity by forming a covalent bond with the enzyme (for example, without limitation, cyclopropyl/aziridinyl tryptophan derivatives).

IDO inhibitors of the instant invention include i) previously established IDO inhibitors, such as, but not limited to: 1-methyl-DL-tryptophan (1MT), β-(3-benzofuranyl)-DL-alanine, beta-(3-benzo(b)thienyl)-DL-alanine, 6-nitro-L-tryptophan, indole 3-carbinol, 3,3'-diindolylmethane, brassinin, epigallocatechin gallate, 5-Br-4-Cl-indoxyl 1,3-diacetate, 9-vinylcarbazole, acemetacin, 5-bromo-DL-tryptophan, 5-bromoindoxyl diacetate, phenyl-TH-DL-trp, propenyl-TH-DL-trp, and methyl-TH-DL-trp; and ii) the novel IDO inhibitors described in the instant invention.

A "signal transduction inhibitor" is an agent that selectively inhibits vital step(s) in signaling pathways, in the normal function of cancer cells, and thereby leading to apoptosis.

Signal transduction inhibitors (STIs) of the instant invention include, but are not limited to, (i) bcr/abl

kinase inhibitors such as, for example, STI 571 (Gleevec); (ii) epidermal growth factor (EGF) receptor inhibitors such as, for example, kinase inhibitors (Iressa, SSI-774) and antibodies (Imclone: C225 [Goldstein et al. (1995), *Clin Cancer Res.* 1:1311-1318], and Abgenix: ABX-EGF); (iii) her-2/neu receptor inhibitors such as, for example, Herceptin™ (trastuzumab), and farnesyl transferase inhibitors (FTI) such as, for example, L-744,832 (Kohl et al. (1995), *Nat Med.* 1(8):792-797); (iv) inhibitors of Akt family kinases or the Akt pathway, such as, for example, rapamycin (see, for example, Sekulic et al. (2000) Cancer Res. 60:3504-3513); (v) cell cycle kinase inhibitors such as, for example, flavopiridol and UCN-01 (see, for example, Sausville (2003) Curr. Med. Chem. Anti-Canc Agents 3:47-56); and (vi) phosphatidyl inositol kinase inhibitors such as, for example, LY294002 (see, for example, Vlahos et al. (1994) J. Biol. Chem. 269:5241-5248).

A "therapeutically effective amount" of a compound or a pharmaceutical composition refers to an amount sufficient to modulate tumor growth or metastasis in an animal, especially a human, including without limitation decreasing tumor growth or size or preventing formation of tumor growth in an animal lacking any tumor formation prior to administration, i.e., prophylactic administration.

"Pharmaceutically acceptable" indicates approval by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

A "carrier" refers to, for example, a diluent, adjuvant, excipient, auxilliary agent or vehicle with which an active agent of the present invention is

administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

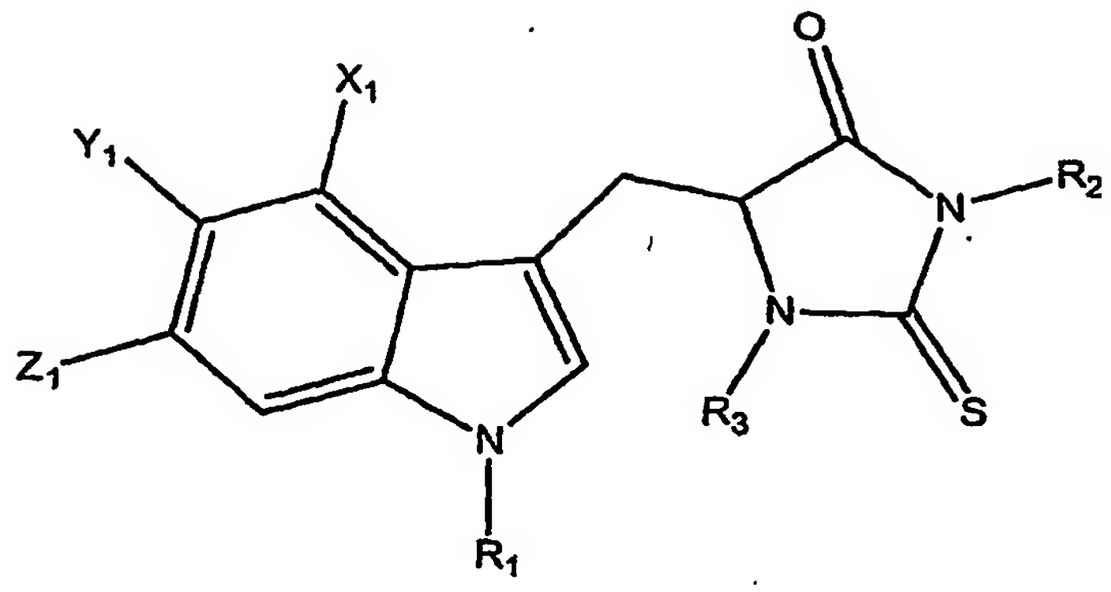
"Concurrently" means (1) simultaneously in time, or (2) at different times during the course of a common treatment schedule.

"Sequentially" refers to the administration of one component of the method followed by administration of the other component. After administration of one component, the next component can be administered substantially immediately after the first component, or the next component can be administered after an effective time period after the first component; the effective time period is the amount of time given for realization of maximum benefit from the administration of the first component.

II. Novel Compounds Exhibiting IDO Inhibitory Activity and Methods of Use

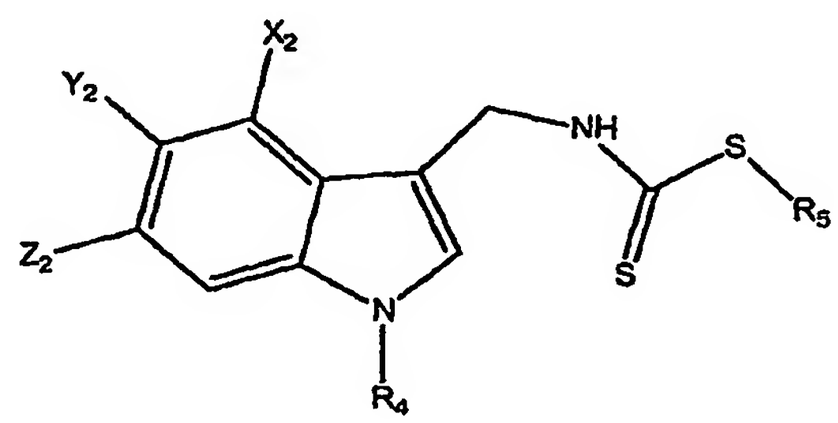
In accordance with the instant invention, novel compounds of the following formulas, which are capable of inhibiting IDO activity and thereby suppressing tumor growth, are provided:

formula (I):



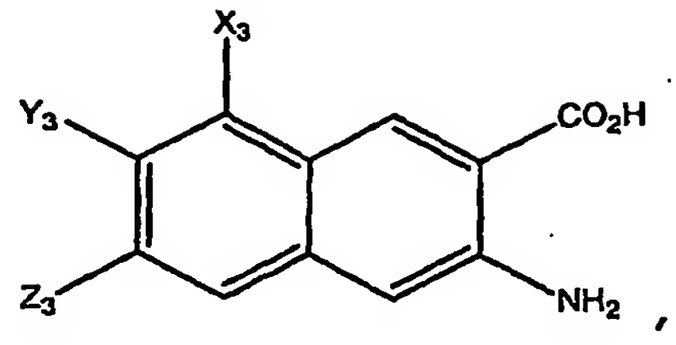
wherein X_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_1 is H or CH_3; R_2 is selected from the group consisting of H, alkyl and aryl; and R_3 is selected from the group consisting of H, alkyl and aryl;

formula (II):



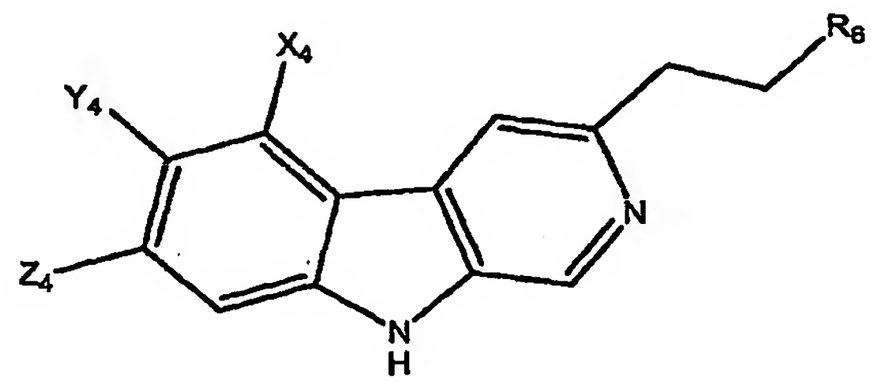
wherein X_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_4 is H or CH_3; and R_5 is selected from the group consisting of H, alkyl and aryl;

formula (III):



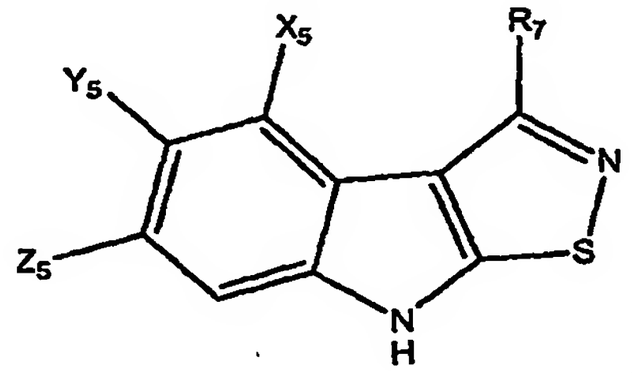
wherein X_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and Z_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl;

formula (IV):



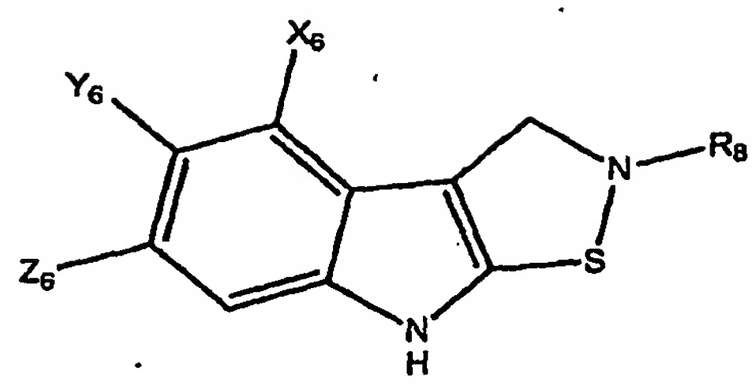
wherein X_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_4 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_6 is alkyl or aryl;

formula (V):



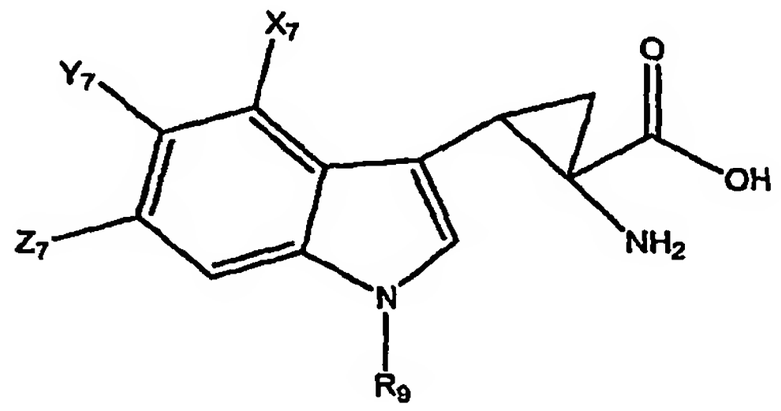
wherein X_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_5 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_7 is alkyl or aryl;

formula (VI):



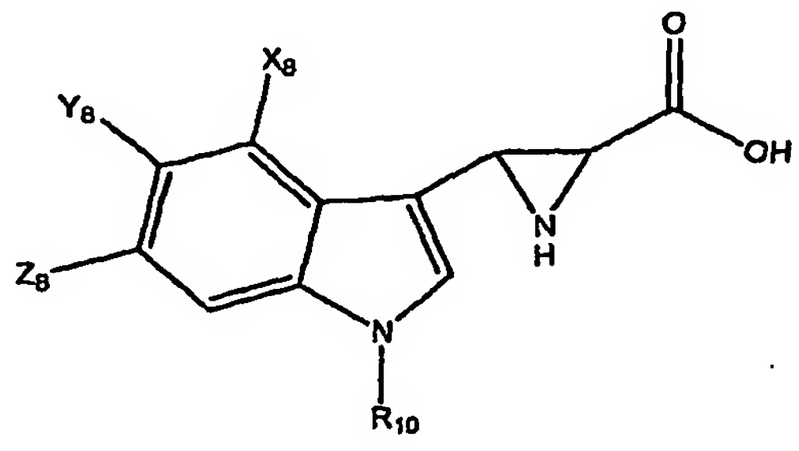
wherein X_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_6 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_8 is alkyl or aryl;

formula (VII):



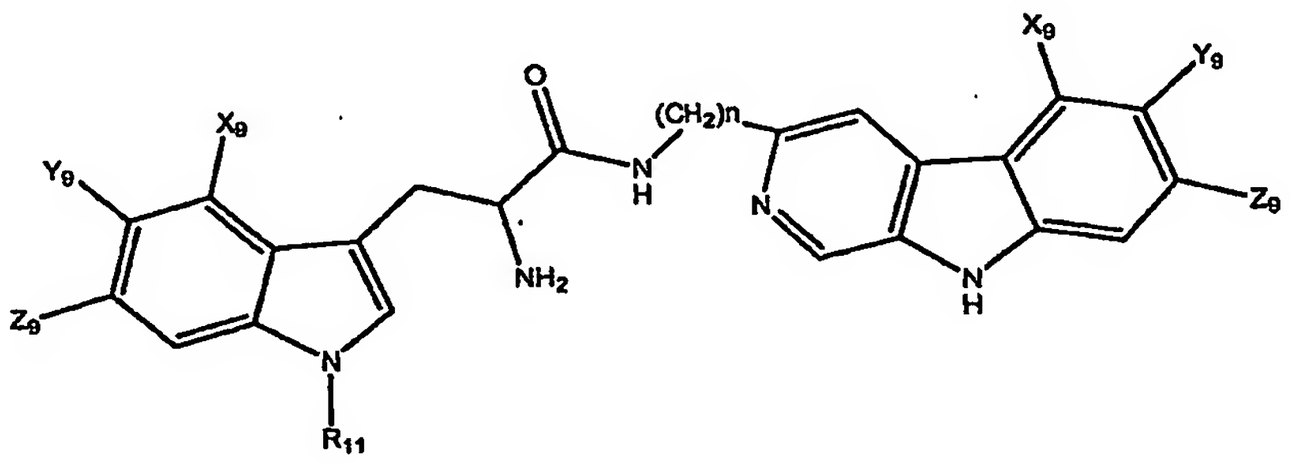
wherein X_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_9 is H or CH_3;

formula (VIII):



wherein X_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{10} is H or CH_3; and

formula (IX):



wherein X_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_9 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_{11} is H or CH_3; and n is about 1 to about 10.

The compounds of formulas (I)-(III) are believed to competitively inhibit IDO activity, while the compounds of formulas (IV)-(V) likely inhibit IDO activity noncompetitively.

The present invention also provides pharmaceutical compositions comprising at least one of these IDO inhibitors having a formula selected from formulas (I)-(IX) in a pharmaceutically acceptable carrier. Such a pharmaceutical composition may be administered, in a therapeutically effective amount, to a patient in need thereof for the treatment of cancer.

Moreover, the present invention provides a method for the treatment of cancer by administering to a patient, in need thereof, a therapeutically effective

amount of at least one IDO inhibitor having the formula selected from formulas (I)-(IX).

Cancers that may be treated using the present protocol include, but are not limited to: cancers of the prostate, colorectum, pancreas, cervix, stomach, endometrium,, brain, liver, bladder, ovary, testis, head, neck, skin (including melanoma and basal carcinoma), mesothelial lining, white blood cell (including lymphoma and leukemia) esophagus, breast, muscle, connective tissue, lung (including small-cell lung carcinoma and non-small-cell carcinoma), adrenal gland, thyroid, kidney, or bone; glioblastoma, mesothelioma, renal cell carcinoma, gastric carcinoma, sarcoma, choriocarcinoma, cutaneous basocellular carcinoma, and testicular seminoma.

III. Combinatorial Therapy for the Treatment of Cancer

The present invention also provides a superior method for tumor suppression. In accordance with the present invention, it has been discovered that the combination of an IDO inhibitor with a signal transduction inhibitor (STI) act synergistically to suppress tumor growth. Accordingly, the present invention provides a pharmaceutical composition for the treatment of cancer in a patient comprising at least one IDO inhibitor and at least one STI in a pharmaceutically acceptable carrier. Also provided is a method for treating cancer in a patient by administering an effective amount of at least one IDO inhibitor in combination with at least one STI. Suitable IDO inhibitors include any compound which exhibits IDO inhibitory activity including compounds having a formula selected from formulas (I)-(IX). Suitable STIs, as noted hereinabove, include, but are not limited to: (i) bcr/abl

kinase inhibitors such as, for example, STI 571 (Gleevec); (ii) epidermal growth factor (EGF) receptor inhibitors such as, for example, kinase inhibitors (Iressa, SSI-774) and antibodies (Imclone: C225 [Goldstein et al. (1995), *Clin Cancer Res.* 1:1311-1318], and Abgenix: ABX-EGF); (iii) her-2/neu receptor inhibitors such as, for example, Herceptin™ (trastuzumab) and farnesyl transferase inhibitors (FTI) such as, for example, L-744,832 (Kohl et al. (1995), *Nat Med.* 1(8):792-797); (iv) inhibitors of Akt family kinases or the Akt pathway, such as, for example, rapamycin (see, for example, Sekulic et al. (2000) Cancer Res. 60:3504-3513); (v) cell cycle kinase inhibitors such as, for example, flavopiridol and UCN-01 (see, for example, Sausville (2003) Curr. Med. Chem. Anti-Canc Agents 3:47-56); and (vi) phosphatidyl inositol kinase inhibitors such as, for example, LY294002 (see, for example, Vlahos et al. (1994) J. Biol. Chem. 269:5241-5248).

In a specific embodiment of the present invention, the at least one IDO inhibitor and at least one STI may be administered to the patient concurrently or sequentially. In other words, the at least one IDO inhibitor may be administered first, the at least one STI may be administered first, or the at least one IDO inhibitor and the at least one STI may be administered at the same time. Additionally, when more than one IDO inhibitor and/or STI is used, the compounds may be administered in any order.

Cancers that may be treated using the present combinatorial protocol include, but are not limited to: cancers of the prostate, colorectum, pancreas, cervix, stomach, endometrium,, brain, liver, bladder, ovary, testis, head, neck, skin (including melanoma and basal carcinoma), mesothelial lining, white blood cell

(including lymphoma and leukemia) esophagus, breast, muscle, connective tissue, lung (including small-cell lung carcinoma and non-small-cell carcinoma), adrenal gland, thyroid, kidney, or bone; glioblastoma, mesothelioma, renal cell carcinoma, gastric carcinoma, sarcoma, choriocarcinoma, cutaneous basocellular carcinoma, and testicular seminoma.

In addition to IDO, other molecules are known to be involved in immunomodulation. These other molecules may also be potential targets for suppressing tumor growth in cancer patients. Accordingly, the present invention also provides combinatorial methods of treating cancer patients by the administration at least one immunomodulator other than an IDO inhibitor in conjunction with at least one chemotherapeutic agent. Suitable immunomodulators that may be used in the present invention include, without limitation: costimulatory molecules, such as, CD40L, B7, and B7RP1; activating monoclonal antibodies (mAbs) to costimulatory receptors, such as, ant-CD40, anti-CD38, anti-ICOS, and 4-IBB ligand; dendritic cell antigen loading (*in vitro* or *in vivo*); dendritic cell cancer vaccine; cytokines/chemokines, such as, IL1, IL2, IL12, IL18, ELC/CCL19, SLC/CCL21, MCP-1, IL-4, IL-18, TNF, IL-15, MDC, IFNa/b, M-CSF, IL-3, GM-CSF, IL-13, and anti-IL-10; bacterial lipopolysaccharides (LPS); and immune-stimulatory oligonucleotides (e.g., poly CpG DNA (see, for example, Verthelyi and Zeuner (2003) Tr. Immunol. 24:519-522)). Suitable chemotherapeutic agents include, but are not limited to, cytotoxic chemotherapeutic agents and signal transduction inhibitors (STIs).

IV. Combinatorial Therapy for the Treatment of Chronic Viral Infections

The present invention also provides a method for treating a chronic viral infection by a combination protocol comprising administration of an IDO inhibitor with a chemotherapeutic agent. Additionally, the method also comprises administering an antiviral agent (i.e., an agent which can treat a viral infection) in coordination with the IDO inhibitor and chemotherapeutic agent.

Accordingly, the present invention provides a pharmaceutical composition for the treatment of a chronic viral infection in a patient comprising at least one IDO inhibitor, at least one cancer therapeutic drug in a pharmaceutically acceptable carrier, and, optionally, at least one antiviral agent. Also provided is a method for treating a chronic viral infection in a patient by administering an effective amount of at least one IDO inhibitor in combination with at least one chemotherapeutic agent and, optionally, at least one antiviral agent.

Suitable IDO inhibitors include any compound which exhibits IDO inhibitory activity including compounds having a formula selected from formulas (I)-(IX).

Suitable chemotherapeutic agents are any compounds that exhibit anticancer activity including, but are not limited to: alkylating agents (e.g., nitrogen mustards such as chlorambucil, cyclophosphamide, isofamide, mechlorethamine, melphalan, and uracil mustard; aziridines such as thiotepa; methanesulphonate esters such as busulfan; nitroso ureas such as carmustine, lomustine, and streptozocin; platinum complexes such as cisplatin and carboplatin; bioreductive alkylators such as mitomycin, procarbazine, dacarbazine and altretamine); DNA strand-breakage agents (e.g., bleomycin);

topoisomerase II inhibitors (e.g., amsacrine, dactinomycin, daunorubicin, idarubicin, mitoxantrone, doxorubicin, etoposide, and teniposide); DNA minor groove binding agents (e.g., plicamydin); antimetabolites (e.g., folate antagonists such as methotrexate and trimetrexate; pyrimidine antagonists such as fluorouracil, fluorodeoxyuridine, CB3717, azacitidine, cytarabine, and floxuridine; purine antagonists such as mercaptopurine, 6-thioguanine, fludarabine, pentostatin; asparginase; and ribonucleotide reductase inhibitors such as hydroxyurea); tubulin interactive agents (e.g., vincristine, vinblastine, and paclitaxel (Taxol)); hormonal agents (e.g., estrogens; conjugated estrogens; ethinyl estradiol; diethylstilbesterol; chlortrianisen; idenestrol; progestins such as hydroxyprogesterone caproate, medroxyprogesterone, and megestrol; and androgens such as testosterone, testosterone propionate, fluoxymesterone, and methyltestosterone); adrenal corticosteroids (e.g., prednisone, dexamethasone, methylprednisolone, and prednisolone); leutinizing hormone releasing agents or gonadotropin-releasing hormone antagonists (e.g., leuprolide acetate and goserelin acetate); and antihormonal antigens (e.g., tamoxifen, antiandrogen agents such as flutamide; and antiadrenal agents such as mitotane and aminoglutethimide). Preferably, the chemotheraputic agent is selected from the group consisting of: placitaxel (Taxol®), cisplatin, docetaxol, carboplatin, vincristine, vinblastine, methotrexate, cyclophosphamide, CPT-11, 5-fluorouracil (5-FU), gemcitabine, estramustine, carmustine, adriamycin (doxorubicin), etoposide, arsenic trioxide, irinotecan, and epothilone derivatives.

Suitable antiviral agents include, without limitation: acyclovir; gangcyclovir; foscarnet;

ribavirin; and antiretrovirals such as, for example, nucleoside analogue reverse transcriptase inhibitors (e.g., azidothymidine (AZT), ddI, ddC, 3TC, d4T), non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, nevirapine), nucleotide analogue reverse transcriptase inhibitors, and protease inhibitors.

In a specific embodiment of the present invention, the at least one IDO inhibitor and at least one chemotherapeutic agent may be administered to the patient concurrently or sequentially. In other words, the at least one IDO inhibitor may be administered first, the at least one chemotherapeutic agent may be administered first, or the at least one IDO inhibitor and the at least one STI may be administered at the same time. Additionally, when more than one IDO inhibitor and/or chemotherapeutic agent is used, the compounds may be administered in any order. Similarly, the antiviral agent may also be added at any point.

The compounds of this combination treatment may also be administered for localized infections. Specifically, the at least one IDO inhibitor, at least one chemotherapeutic agent, and, optionally, at least one antiviral agent may be administered to treat skin infections such as shingles and warts. The compounds may be administered in any pharmaceutically acceptable topical carrier including, without limitation: gels, creams, lotions, ointments, powders, aerosols and other conventional forms for applying medication to the skin.

Chronic viral infections that may be treated using the present combinatorial treatment include, but are not limited to, diseases caused by: hepatitis C virus (HCV), human papilloma virus (HPV), cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV),

varicella zoster virus, coxsackie virus, human immunodeficiency virus (HIV).

Notably, parasitic infections (e.g. malaria) may also be treated by the above methods wherein compounds known to treat the parasitic conditions are optionally added in place of the antiviral agents.

V. Administration of Pharmaceutical Compositions and Compounds

The pharmaceutical compositions of the present invention can be administered by any suitable route, for example, by injection, by oral, pulmonary, nasal or other forms of administration. In general, pharmaceutical compositions of the present invention, comprise, among other things, pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions can include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; and additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol). The compositions can be incorporated into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc., or into liposomes. Such compositions may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of components of a pharmaceutical composition of the present invention. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 which are herein incorporated by reference. The pharmaceutical composition of the present invention can be prepared, for

example, in liquid form, or can be in dried powder form (e.g., lyophilized). Particular methods of administering pharmaceutical compositions are described hereinabove.

In yet another embodiment, the pharmaceutical compositions of the present invention can be delivered in a controlled release system, such as using an intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In a particular embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. (1987) 14:201; Buchwald et al., Surgery (1980) 88:507; Saudek et al., N. Engl. J. Med. (1989) 321:574). In another embodiment, polymeric materials may be employed (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Press: Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley: New York (1984); Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. (1983) 23:61; see also Levy et al., Science (1985) 228:190; During et al., Ann. Neurol. (1989) 25:351; Howard et al., J. Neurosurg. (1989) 71:105). In yet another embodiment, a controlled release system can be placed in proximity of the target tissues of the animal, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, (1984) vol. 2, pp. 115-138). In particular, a controlled release device can be introduced into an animal in proximity of the site of inappropriate immune activation or a tumor. Other controlled release systems are discussed in the review by Langer (Science (1990) 249:1527-1533).

The following examples are provided to illustrate various embodiments of the present invention. They are not intended to limit the invention in any way.

EXAMPLE 1:

Synthesis of Thiohydantoin Derivatives

Overview: Thiohydantoin derivatives, or compounds with formula (I), were identified by screening commercially available tryptophan derivatives. N-Methyl (R_1=H; R_2=CH_3; R_3=H; X_1, Y_1, Z_1=H), N-allyl (R_1=H; R_2=-$CH_2CH=CH_2$; R_3=H; X_1, Y_1, Z_1=H) and N-phenyl (R_1=H; R_2=Ph; R_3=H; X_1, Y_1, Z_1=H) thiohydantoin derivatives demonstrated greater than 50% inhibition and significant selectivity over the structurally distinct enzyme tryptophan 2,3-dioxygenase (TDO2). To further improve inhibitor potency, the focus of the present invention will be on substitution of the indole ring, a procedure which has enhanced potency of tryptophan derivatives in the past. In particular, literature reports indicate that N-1, C-5 and C-6 substitution of the indole ring will afford more potent inhibitors (Cady and Sono (1991) Arch. Biochem. Biophys., 291:326-33; Munn, D.H., et al. (1998) Science, 281:1191-3; Peterson, A.C., et al. (1994) Med. Chem. Res., 3:531-544; Southan, M.D., et al. (1996) Med. Chem. Res., 6: 343-352). Additionally, while C-4 halide derivatives have not been reported in the literature (Southan et al.), the instant invention has identified 5-bromo-4-chloroindoxyl 1,3-diacetate as a potent inhibitor (greater than 50% inhibition of IDO at 250 μM).

Synthesis: Thiohydantoin derivatives will be synthesized via an Erlenmeyer-Plochl azlactone-type condensation reaction between an indole-3-carboxaldehyde and thiohydantoin **1** (Figure 1; Djura and Faulkner (1980) J. Org. Chem., 45:735-7; Guella, G., et al. (1988) Helv.

Chim. Acta, 71:773-82; Guella, G., et al. (1989) Helv. Chim. Acta, 72:1444-50; Crawford and Little (1959) J. Chem. Soc., 729-731; Julian and Sturgis (1935) J. Am. Chem. Soc., 1126-28). A mixture of conjugated alkene stereoisomers **3** will likely result and these products can be tested as planar analogues of the thiohydantoins. Reduction of the conjugated alkene in **3** can be performed by nucleophilic reductants (e.g. $NaBH_4$, $Li(s\text{-}Bu)_3BH$, and $[(Ph_3P)CuH]_6$) as the presence of sulfur will prohibit more commonly used catalytic hydrogenation methods.

The thiohydantoins can be synthesized by the reaction of, for example, glycine methyl ester or glycine ethyl ester with alkyl isothiocyanates (Figure 1; Sim and Ganesan (1997) J. Org. Chem., 62:3230-35). Notably, this method of thiohydantoin synthesis allows for a variety of alkyl groups to be incorporated at the N-1 nitrogen atom via reductive amination (Sim and Ganesan (1997) J. Org. Chem., 62:3230-35) and N-3 nitrogen atom depending on the choice of isothiocyanate reagent.

Based on previous IDO inhibitor studies, a variety of halo-substituted indole-3-carboxaldehydes can be used in the condensation reactions with thiohydantoins. 5-Bromo- and 5-chloroindole-3-carboxaldehyde are commercially available. Substitution in the C-4 position of the indole-3-carboxaldehyde can be accomplished by thallation-halogenation of indole-3-carboxaldehydes **5** (Figure 2; Somei, M., et al. (1984) Heterocycles, 22(4):797-801; Ohta, T., et al. (1987) Hetereocycles 26:2817-22; Somei, M., et al. (1985) Chem. Pharm. Bull. 33:3696-708). N-methylation of the indole-3-carboxaldehydes **6** can be performed by reacting with a dimethyl carbonate (Jiang, X., et al. (2001) Org. Proc. Res. Dev., 5:604-8).

Generation of 6-halo-indole-3-carboxaldehydes can proceed via 6-aminoindole, which is readily synthesized from commercially available 2,4-dinitrotoluene via a Leimgruber-Batcho indole synthesis (Figure 3; Batcho and Leimgruber (1990) Org. Syn. Coll., 3:34). The 6-amino group can be protected as an acetamide. Vilsmeier formylation of the C-3 position can provide the 6-substituted indole-3-carboxaldehyde **10** (Smith, G. F. (1954) J. Chem. Soc., 3842-6; James and Snyder (1963) Org. Syn. Coll., 4:539). The presence of an electron-releasing acetamide group can enhance the efficiency of the Vilsmeter formylation. Methylation of the indole nitrogen can proceed as described previously. The 6-amino group will be deprotected under acid reflux conditions and then the amine **12** can be transformed into a halogen via Sandmeyer or Schiemann reaction (Somei, M., et al. (1985) Chem. Pharm. Bull., 33:3696-708; Somei and Tsuchiya (1981) Chem. Pharm. Bull., 29:3145-57; Moriya, T., et al. (1975) Bull. Chem. Soc. Jpn., 48:2217-8) or oxidized to a nitro group with a peroxyacid (Pagano and Emmons, Org. Syn. Coll., 5:367). Problems with side reactions involving the 3-carboxaldehyde during the Sandmeyer, Schiemann or amine oxidation reactions can be overcome by altering the sequence to install the 3-carboxaldehyde and methylate at the N-1 position later.

Derivatives with substitution at both the 5 and 6 positions will be possible via electrophilic aromatic substitution of **14** (Figure 4). Nitration of 1-methyl-indole-3-carboxaldehyde has reportedly afforded a 93% yield of a mixture of the 5-nitro and 6-nitro products (Da Settimo and Saettone (1965) Tetrahedron 21:1923-9). Use of the 6-acetamido derivative prevents nitration at the 6 position and further activates the 5 position to eletrophilic aromatic substitution. In addition to

nitration, bromination and chlorination may also be employed and thereby allow a variety of 5,6-disubstituted indole-3-carboxaldehydes to be synthesized. In addition, thallation-halogenation (Somei, M., et al. (1984) Heterocycles, 22(4):797-801; Ohta, T., et al. (1987) Heterocycles, 26:2817-22; Somei, M., et al. (1985) Chem. Pharm. Bull., 33:3696-708) of the 5,6-disubstituted indole-3-carboxaldehydes **15** permits functionalization of the C-4 position. Furthermore, following the methods elaborated in Scheme 3 (Figure 3), the C-4 acetamide group can be modified. When combined, these procedures allow complex polysubstituted indole-3-carboxaldehydes to be obtained in a highly efficient manner.

Notably, IDO demonstrates a preference for L-tryptophan (Peterson, A. C., et al. (1994) Med. Chem. Res., 3:531-544), but will also accept D-tryptophan as a substrate (Sono, M. (1989) Biochemistry, 28:5400-7). Therefore, an enantiomerically pure product may not be absolutely required.

An alternative approach for the synthesis of thiohydantoin derivatives involves the condensation of **2** with the ethyl half ester of acetamidomalonic acid (Figure 5; Hengartner, U., et al. (1979) J. Org. Chem., 44:3741-7). Hydrogenation with Wilkinson's catalyst generates **19** (Horwell, D.C., et al. (1994) J. Org. Chem., 59:4418-23). Hydrolysis of the acetamide and ethyl ester affords the tryptophan analogue **20**. Reaction with alkyl isothiocyanate affords the thiohydantoin product (Cejpek, K., et al. (2000) J. Agric. Food. Chem., 48:3560-5; Mizrach and Polonska (1987) Khim. Farm. Zh., 21:322-8), although it may be more efficient to perform the isothiocyanate reaction on the analogous amino ester (Sim and Ganesan (1997) J. Org. Chem., 62:3230-35).

A potentially important benefit of the alternative path is the ability to obtain an enantiomeriaclly enriched product. Several asymmetric hydrogenations of related dehydrotryptopha compounds have been reported (Hengartner, U., et al. (1979) J. Org. Chem., 44:3741-7; Knowles, W.S., et al. (1975) J. Am. Chem. Soc., 97:2567-8). Therefore, substitution of the triphenylphophine ligands of Wilkinson's catalyst with chiral phosphine ligands can permit stereoselective synthesis of the L isomer of the tryptophan analogue.

EXAMPLE 2:

Synthesis of Brassinin Derivatives

Overview: Brassinin and related phytoalexins have demonstrated anticancer properties, reportedly due to preventative effects achieved by carcinogen detoxification (Park and Pezzuto (2002) Cancer Metathesis Rev., 21:231-255; Mehta, R.G., et al. (1995) Carcinogenesis 16:399-404; Mehta, R.G., et al. (1994) Anticancer Research 14:1209-1213). Interestingly, brassilexin, a related phytoalexin, is reportedly a noncompetitive inhibitor of IDO (Peterson, A.C., et al. (1993) Med. Chem. Res., 3:473-482). In addition, preliminary work indicates brassinin is a competitive inhibitor of IDO. To date, there have been no studies of IDO inhibition with brassinin derivatives (i.e. compounds having the formula of formula (II) or brassilexin derivatives (i.e., compounds having the formula of formula (V) or (VI)). The structural similarity of brassinin to tryptophan and its identification as a competitive inhibitor suggest derivatization similar to tryptophan-based inhibitors already reported.

Synthesis: Indole-3-carboxaldehydes discussed above (Figures 2-4) can be employed to generate brassinin

derivatives, i.e., IDO inhibitors having the formula of formula (II). The indole-3-carboxaldehydes 2 can be transformed into 3-aminomethyl derivatives 22 by reductive amination with hydroxylamine (Figure 6). The 3-aminomethylindole derivatives may be unstable (Kutschy, P., et al. (1991) Synlett, 289-290; Kutschy, P., et al. (1998) Tet. 54:3549-66) and therefore will immediately be treated with carbon disulfide an then methyl iodide to generate brassinin derivatives with substitution in benzene ring (Takasugi, M., et al. (1988) Bull. Chem. Soc. Jpn. 61:285; Pedras, M.S.C., et al. (1992) Life Science Advances (Phytochemistry), 11:1; Mehta, R. G., et al. (1995) Carcinogenesis, 16(2):399-404).

EXAMPLE 3:

Synthesis of β-Carboline Derivatives

Overview: β-Carboline or norharman derivatives, i.e., compounds having the formula of formula (IV), have been previously reported (Sono and Cady (1989) Biochemistry, 28:5392-5399; Peterson, A.C., et al. (1993) Med. Chem. Res., 3:473-482; Eguchi, N., et al. (1984) Arch. Biochem. Biophys., 232(2):602-609). However, analogues of the most active derivative, 3-butyl-β-carboline, have not been reported. Notably, substitution at the C-6 position (-F and -N=C=S) of the β-carboline core yielded several similarly active derivatives, but analogues that combine the C-3 and C-6 substitution were not tested; nor were any other substitutions larger than the C-3 butyl of the β-carboline explored (Peterson, A.C., et al. (1993) Med. Chem. Res. 3:473-482). β-carboline derivatives with substitution at the C-5, 7, and 8 position have also not been reported. Of particular interest is the reported mechanism of action of β-carboline derivatives as non-competitive inhibitors,

e.g., competition with oxygen for a binding site on the heme iron of the ferrous enzyme (Sono and Cady (1989) Biochemistry, 28:5392-5399).

Synthetic: The commercially availability of ethyl β-carboline-3-carboxylate **24** makes chemical modifications of this structure attractive for the synthsis of β-carboline derivatives (Figure 7). Nitration (Settimj, G., et al. (1988) J. Heterocyclic Chem. 25:1391-7) and iodination (Huth, A., et al. (1987) Tet. 43:1071-4) of the C-6 position of **24** has been accomplished in good yield. In addition, regioselective bromination (Ponce and Erra-Balsells (2001) J. Heterocyclic Chem. 38:1087-1095; Kardono, L. B. S., et al. (1991) J. Nat. Prod. 54:1360-7) and chlorination (Ponce, M.A., et al. (2003) J. Heterocyclic Chem. 40:419-426) procedures for β-carboline have also been reported. Reduction of the C-6 nitration product has been accomplished (Settimj, G., et al. (1988) J. Heterocyclic Chem. 25:1391-7) and the resulting amine has been used to direct bromination in the C-5 position of the β-carboline (Huth, A., et al. (1987) Tet. 43:1071-4). These reactions will facilitate the synthesis of C-5 and C-6 substituted β-carboline derivatives.

Derivatization of the C-3 position may be performed via the C-3 carboxaldehyde (Figure 8). Chemoselective reduction (or reduction to the alcohol and chemoselective oxidation) of the C-3 ester of **24** with DIBAL affords the C-3 carboxaldehyde. Addition of organolithium or Grignard reagents to the aldehyde affords alcohol derivatives **29**. Dehydration of the alcohol affords an alkene **30** that can be selectively reduced to yield the C-3 alkyl group of variable length depending on the choice of organometallic reagent. The alcohol and alkene

intermediates may also be tested. Alternatively, Wittig reaction with the carboxaldehyde can afford the alkene.

An alternative approach to β-carboline derivatives involves cyclization and oxidation of tryptophan derivatives **32** (Figure 9; Haffer, G., et al. (1998) Heterocycles 48(5):993-8). The tryptophan derivatives discussed earlier (Figures 2-4) are amenable to cyclization to form the pyrido-indole structure. One advantage in using this procedure is the ability to create potential β-carboline based IDO inhibitors with functionalization in the C-7 position of β-carboline.

EXAMPLE 4:

Synthesis of 3-Amino-2-Naphthoic Acid Derivatives

Overview: In 1994, Peterson and co-workers reported 3-amino-2-naphthoic acid to be the most potent IDO inhibitor amongst a selection of tryptophan derivatives and related compounds (Peterson, A.C., et al. (1994) Med. Chem. Res. 3:531-544). Notably, there were no other derivatives of 3-amino-2-napthoic acid reported in the article, nor have other tests with this structure of related derivatives ever been reported, despite the fact that the compound was more potent than the prototypical IDO inhibitor L-1-methyl-tryptophan (1MT). Since 3-amino-naphthoic acid is a competitive inhibitor, derivatives with substituents in the C-6, C-7, and C-8 positions of the naphthalene core (analogous to the C-4, C-5, and C-6 positions of the indole ring in tryptophan) may provide a superior IDO inhibitor.

Synthesis: Although there exist many methods to synthesize naphthalene compounds (de Koning, C.B., et al.(2003) Tet. 59:7-36), the synthesis of asymmetrically substituted naphthalenes with substituents in both rings remains a challenge. However, substituted 3-amino-2-

naphthoic acids can be generated by first performing a benzannulation of substituted phthaldehydes (Kienzle, F. (1980) Helv. Chim. Acta 63:2364-9; Singh and Khade (2002) Bioconj. Chem. 13:1286-91). The rapid synthsis of 3-amino-7-bromo-2-naphthoic acid **36** demonstrates the efficiency of this methodology (Figure 10).

The phthaldehyde **34** will be synthesized from 4-bromo-o-xylene or dimethyl phthalate. Ethyl 3-nitropropionate can be synthesized in one step from silver nitrite and ethyl 3-bromopropionate (Belikov, V.M. (1956) Izv. Akad. Nauk., S.S.S.R.; Otdel. Khim. Nauk 855-62; Chemical abstract (1957) 51:1837j). Condensation of the two affords a mixture of 6-bromo and 7-bromo 3-nitro-2-naphthoic acids **35**. Reduction of the nitro group and hydrolysis of the ester affords the brominated 3-amino-2-naphthoic acids. The two regioisomers may be separated at some point in the synthesis, but both compounds can also be tested and the rapid manner in which the two are assembled likely outweighs any inconveniences of the regioisomeric mixture.

The synthesis of more substituted 3-amino-2-naphthoic acids allows for regiocontrol through the use of electron donating groups in place of the bromine (Figure 11). The phthaldehydes **37** can be generated from either 3,4-dimethylaniline or dimethyl phthalate. Electrophilic aromatic substitution of the amino or acetamido phthaldehyde precursors allows for the incorporation of groups in the C-6 position of the 3-amino-2-naphthoic acid. The benzannulation reaction is regioselective due to electron releasing acetamido group (Kienzle, F. (1980) Helv. Chim. Acta 63:2364-9). After benzannulation, the 7-acetamido or amino group allows for the efficient substitution at C-8 via electrophilic aromatic substitution reactions. Upon deprotection, the

7-amino group can undergo diazotization and Sandmeyer or Schiemann reaction to afford a variety of substituents. Nitro group reduction and ester hydrolysis affords the 3-amino-2-naphthoic acid derivatives, i.e. compounds of formula (III) for testing.

As an alternative method, methoxy phthaldehydes 43 (Z=H) have demonstrated considerable control in condensation reactions with 3-nitropropionates (Figure 12; Kienzle, F. (1980) Helv. Chim. Acta 63:2364-9). The methoxy group directs electrophilic aromatic substitution reactions to ortho positions, however to transform the methoxy group into an amine and subsequently to a halogen, the Buchwald-Hartwig amination methodology (Wolfe, J.P., et al. (2000) J. Org. Chem. 65:1158-74; Wolfe and Buchwald (1997) J. Org. Chem. 62:1264-7; Louie, J., et al. (1997) J. Org. Chem. 62:1268-73; Hartwig, J.F. (1998) Angew. Chem. Int. Ed. Engl. 37:2046-67) can be performed. Conversion of the methoxy to triflate **45** allows for amination, but carboxylic esters are not compatible with this process due to the strongly basic conditions. Consequently, 3-nitro-propanenitrile, which can be synthesized similarly to ethyl 3-nitropropionate but with 3-bromopropionitrile as starting material, can be used in the condensation and the cyano group can be hydrolyzed at the end of the synthsis.

EXAMPLE 5:

Synthesis of Brassilexin Derivatives

Brassilexin derivatives, compounds of formula (V) or (VI), wherein R_7 or R_8 is H can be synthesized as shown in Figure 13 (see, for example, Devys and Barbier (1993) Org. Prep. Proc. Int. 25:344-346).

The synthesis scheme for brasilexin derivatives, wherein R_7 or R_8 is not H, is shown in Figures 14 and 15

(see, for example, Yeung et al. (2002) Tet. Lett. 43:5793-5795).

EXAMPLE 6:

Synthesis of Cyclopropyl/Aziridinyl Tryptophan Derivatives

The schemes for synthesizing cyclopropyl/aziridinyl tryptophan derivatives, compounds of formula (VII) or (VIII), are shown in Figures 16 and 17 (see, for example, Donati et al. (1996) Tetrahedron 52:9901-9908; Ishikawa et al. (2001) J. Am. Chem. Soc. 123:7705-7706).

EXAMPLE 7:

Synthesis of Tethered Competitive/Noncompetitive Derivatives

Figure 18 shows the scheme for the synthesis of tethered competitive/noncompetitive derivatives, i.e. compounds of formula (IX).

EXAMPLE 8:

Evaluation of Novel IDO Inhibitors

1. Biochemical Evaluation of Novel IDO Inhibitors:

Overview: The biochemistry of IDO is well established, the enzyme having first been isolated in 1963 (Higuchi, K., et al. (1963) Federation Proc. 22:243 (abstr.); Shimizu, T., et al.(1978) J. Biol. Chem. 253:4700-6). IDO is a monomeric, haem-containing oxidoreductase with a molecular weight of approximately 41 kDa. To maintain the active ferrous form during *in vitro* catalysis, the enzyme requires methylene blue in combination with either superoxide or a reductant such as ascorbic acid. *In vivo*, it is suggested that a flavin or tetrahydrobiopterin may fulfill the role of the methylene blue dye and that there is likely to be a specific site

for noncompetitive IDO inhibitors. Active enzyme can be produced by expressing the cloned, His-tagged version of the mammalian gene in bacteria (Littlejohn, T.K., et al. (2000) Prot. Exp. Purif. 19:22-29). This provides a convenient source of enzyme for biochemical analysis. A conventional biochemical assay for IDO activity based on spectaphotometric measurement of the production kynurenine (the hydrolysis product of N-formyl-kynurenine) from tryptophan (Daubener, W., et al. (1994) J. Immunol. Methods 168:39-47) is used as the read-out for both the enzymatic and cell-based assays. The enzymatic assay provides a facile, high-throughput screen for identifying compounds with IDO inhibitory activity. This assay is also used to determine Ki values for specific compounds, which is important for the development of SAR (structure activity relationship) around the different compound series. The cell-based assay both confirms the IDO inhibitory activity of identified compounds, and addresses the initial issue of bioavailability - the ability of compounds to inhibit intracellular IDO. Specificity for IDO inhibition is examined in the cell-based assay by comparing against the other known tryptophan catabolizing enzyme tryptophan dioxygenase (TDO, also referred to in the literature as TDO2).

Methods: cDNA clones for both human and mouse IDO have been isolated and verified by sequencing. To prepare enzyme for biochemical studies, C-terminal His-tagged IDO protein can be produced in *E.coli* using the IPTG-inducible pET5a vector system and isolated over a nickel column. The yield of the partially purified protein can be verified by gel electrophoresis and the concentration estimated by comparison to protein standards. To assay IDO enzymatic activity, a 96-well

plate spectraphotometric assay for kynurenine production can be run following published procedures (Littlejohn, T.K., et al. (2000) Prot. Exp. Purif. 19:22-29; Takikawa, O., et al. (1988) J. Biol. Chem. 263:2041-8). To screen for evidence of IDO inhibitory activity, compounds can be evaluated at a single concentration of, for example, 200 µM against 50 ng of IDO enzyme in 100 µl reaction volumes with tryptophan added at increasing concentrations at, for example, 0, 2, 20, and 200 µM. Kynurenine production can be measured at 1 hour. More extensive enzyme kinetic data can be collected for selected compounds of interest. Best fit Ki value determinations for 1MT (Ki = 34.6 µM) and for MTH-Trp (Ki = 11.4 µM) are shown in Figure 19. These data indicate that the thiohydantoin form directly inhibits IDO enzyme activity with about 3-fold greater potency than is achieved with 1MT.

The following procedure is an example of a cell-based assay. COS-1 cells are transiently transfected with a CMV promoter-driven plasmid expressing IDO cDNA using Lipofectamine 2000 (Invitrogen) as recommended by the manufacturer. A companion set of cells is transiently transfected with TDO-expressing plasmid. 48 hours post-transfection the cells are apportioned into a 96-well format at $6x10^4$ cells per well. The following day the wells are washed and new media (phenol red free) containing 20 µg/ml tryptophan is added together with inhibitor. The reaction is stopped at 5 hours and the supernatant removed and spectraphotometrically assayed for kynurenine as described for the enzyme assay (Littlejohn, T.K., et al. (2000) Prot. Exp. Purif. 19:22-29; Takikawa, O., et al. (1988) J. Biol. Chem. 263:2041-8). To obtain initial confirmation of IDO activity, compounds can be evaluated at a single concentration of, for example, 100 µM. More extensive dose escalation

profiles can be collected for select compounds. EC50 value determinations for 1MT (EC50 = 267 μM) and for MTH-Trp (EC50 = 12.9 μM) are shown in Figure 20. These data indicate that MTH-Trp is substantially more potent against intracellular IDO (~20-fold) than is 1MT.

2. Pharmacodynamic/Pharmacokinetic Evaluation of Novel IDO Inhibitors:

Overview: Intraperitoneal administration of bacterial lipopolysaccharide (LPS) induces IDO activity in a variety of tissues resulting in the production of kynurenine and its release into the bloodstream (Figure 21). Peak kynurenine levels are reached one day after LPS administration (Takikawa, O., et al.(1986) J. Biol. Chem. 261:3648-53; Yoshida, H., et al.(1998) Cell 94:739-750). The pharmacodynamic assay described here is based on measuring serum levels of both kynurenine and tryptophan. Calculating the kynurenine/tryptophan ratio provides an estimate of IDO activity that is independent of baseline tryptophan levels (Fuchs, D., et al.(1991) Immunol. Lett. 28:207-11; Gasse, T., et al.(1994) Eur. J. Clin. Chem. Clin. Biochem. 32:685-9), and this approach to measuring IDO activity has been used frequently in humans. The principle advantage of this approach over the direct assessment of IDO enzymatic activity in tissue is that it is a non-invasive procedure permitting multiple samples to be collected from the same animal. This enables IDO activity to be monitored in a single mouse at multiple time points. Tryptophan and kynurenine levels in the serum can be determined by HPLC analysis. The level of compound in serum can also be determined in the same HPLC run, thus permitting concurrent collection of pharmacokinetic data in a single experiment.

Methods: FVB MMTV-neu male mice at ~8-10 weeks of age can be used to perform the bulk of the pharmacodynamic analysis because their genetic background is the same as that of the MMTV-neu females mice that are used in the mammary gland tumor model to evaluate compound efficacy. *Salmonella minnesota* mutant strain R-595 (*S. minnesota* R) derived LPS has been shown to elicit the most sustained level of kynurenine induction in a comparative analysis of LPS preparations from different bacterial strains (Yoshida, R., et al.(1981) Arch. Biochem. Biophys. 212:629-37). Because it provides the widest window in which to evaluate the impact of IDO inhibitors, this preparation of LPS can be used in the pharmacodynamic assay. The minimum i.p. bolus dose of *S. minnesota* R LPS that elicits maximal IDO activity has been reported to be ~1 mg/kg and maximal IDO activation is reached by ~24 hr. following LPS treatment (Yoshida, R., et al.(1981) Arch. Biochem. Biophys. 212:629-37).

Serum levels of kynurenine and tryptophan will be quantitatively determined by HPLC analysis (Hwu, P., et al.(2000) J Immunol 164:3596-9; Widner, B., et al.(1997) Clin. Chem. 43:2424-6). By this procedure, serum concentrations of at least 1.25 μM kynurenine and 3 μM tryptophan are detected. In unchallenged FVB male mice the serum kynurenine is at or below the limit of detection and serum tryptophan is readily detectable at ~50 μM (Figure 22B). 24 hr after LPS challenge, serum kynurenine is induced to ~6 μM (Figure 22C). 1MT in serum at a concentration of at least 5 μM can also be effectively measured. This is well below the serum levels of ~100 μM 1MT achieved with biologically efficacious dosing of 2 x 140 mg 1MT pellets (Figure 22D).

Compounds can be evaluated first by challenging with LPS and then subsequently administering a bolus dose of compound at the time that the serum kynurenine level plateaus. The kynurenine pool is rapidly turned over with a half-life in serum of less than 10 minutes (Bender, and McCreanor (1982) Biochim. Biophys. Acta 717:56-60; Takikawa, O., et al. (1986) J. Biol. Chem. 261:3648-53) so that pre-existing kynurenine is not expected to unduly mask the impact that IDO inhibition has on kynurenine production. The vehicle chosen for administration can depend in large part on the physical properties of each particular compound. The preferred vehicle is isotonic saline, but this requires that the compound be soluble in aqueous solution. It is anticipated that some compounds may not be sufficiently soluble, in which case the compounds can be administered as a suspension in methocel/tween (0.5% methylcellulose/1% tween 80).

Each experiment can include non-LPS-exposed mice (to determine baseline kynurenine levels against which to compare the other mice) and a set of LPS-exposed mice dosed with vehicle alone (to provide a positive control for IDO activation). Mice can be monitored following LPS administration and immediately euthanized if they present with signs of pronounced endotoxemia (ruffled fur, sluggishness). Each compound can initially be evaluated in mice at a single high i.p. bolus dose in the range of at least 100 mg/kg. Blood will be collected at defined time intervals (for example, 50 µl/sample at 5, 15, 30 min., 1, 2, 4, 6, 8, and 24 hr. following compound administration) for HPLC analysis of kynurenine and tryptophan levels (pharmacodynamic analysis) as well as for the level of compound (pharmacokinetic analysis). From the pharmacokinetic data the peak serum

concentration of compound achieved can be determined as well as the estimated rate of clearance. By comparing the level of compound in serum relative to the kynurenine/tryptophan ratio at various time points, the effective IC_{50} for IDO inhibition *in vivo* can be roughly estimated.

Based on the results of the single dose study, a second dose escalation study can be conducted for every efficacious compound. The study can be, for example, aimed at a maximum dose that achieves 100% IDO inhibition at the peak concentration (if possible) in one cohort of mice and dose additional cohorts with concentrations that decrease in 3-fold stepwise increments to cover a 2 log_{10} range between the highest and lowest doses. Accurate IC_{50} determinations will be extracted from these data. The same approach can be used to test for oral bioavailability of biologically active compounds, first testing each compound at a single maximum concentration p.o. bolus dose and then further evaluating those compounds that exhibit significant oral efficacy in a dose escalation study. To ensure that *in vivo* responsiveness is not subject to sexual dimorphism, a single i.p bolus dose experiment can be carried out in female mice at the calculated IC_{50} dose for each active compound.

EXAMPLE 9:

Combinatorial Treatment of Tumors with an IDO Inhibitor and a Signal Transduction Inhibitor

The MMTVneu transgenic "oncomouse" model of breast cancer was used to measure the effects of IDO inhibitors and STIs on tumor pathophysiology. The MMTVneu transgenic mouse develops aggressive tumors of the mammary gland that resemble poorly differentiated human

ductal carcinomas. In the MMTVneu mouse model, breast cancer is initiated by tissue-specific expression of a mutant form of the HER-2/Neu gene that is activated frequently in aggressive human breast ductal carcinomas. HER-2 is a member of the EGF-R family of cell surface growth factor receptors. Myc is an obligate downstream effector for HER-2/Neu to drive cancer. Female MMTVneu "oncomice" are mated twice to initiate expression from the mouse mammary tumor virus (MMTV) promoter which drives transcription of the Neu/HER2 oncogene in mammary tissue. Mammary tumors arise with a penetrance of >90% in this model system by 5 months of age. MMTVneu "oncomice" bearing similarly sized tumors of ~150 mm^3 were randomly assigned to control or experimental treatment groups. Control mice were implanted with placebo time-release pellets (Innovative Research, Inc., Sarasota, FL). Experimental groups of mice were (1) implanted with 1MT-containing time-release pellets, (2) treated with L-744,832, or (3) implanted with 1MT-containing time-release pellets and treated with L-744,832. L-744,832, which mimics the CaaX motif to which the farnesyl group is added, is a potent and selective inhibitor of farnesyl transferase inhibitor (FTI) (Kohl et al., (1995) *Nat Med.* 1(8):747-748).

The time-release pellets are comprised of a copolymer which is inert and gradually dissolves and breaks down to a non-toxic substance that remains largely localized during the course of the experiment. Time-release pellets impregnated with 1MT release a dose of 10 mg/day for a period of up to 14 days as documented by the commercial vendor (Innovative Research, Inc., Sarasota, FL). Two pellets per mouse were implanted to deliver a total dose of 20 mg/day. Therefore, for a 25 g mouse the total dose is 800 mg/kg/day or 280 mg over a 14

day period. Steady-state levels were reached within 12-24 hours and are maintained throughout the entire period based on the manufacturer's specifications. The delivered dose is effective at eliciting allogenic conceptus rejection (A. Muller, J.B. DuHadaway, G.C. Prendergast, unpublished results) as described by Munn et al. (Science **281**:1191-1193, 1998).

Time-release pellets were introduced subcutaneously on the backs of mice anesthetized by intramuscular injection of ketamin/rompun. Blunt dissection with a hemostat is used to separate the skin from the underlying muscle to create a subcutaneous pocket. One or two biodegradable slow release pellets were implanted within this pocket, rather than directly under the incision in order to prevent mechanical stress and wound dehiscence. The incision was then closed with wound clips. Based on the ability of female mice that have been implanted with placebo time-release pellets to carry pregnancies to term, distress from the procedure appears to be negligible.

The signal transduction inhibitors, e.g., FTI L-744,832 were prepared and delivered to the mice as described in Kohl et al. (Nature Med. (1995) 1:792-797).

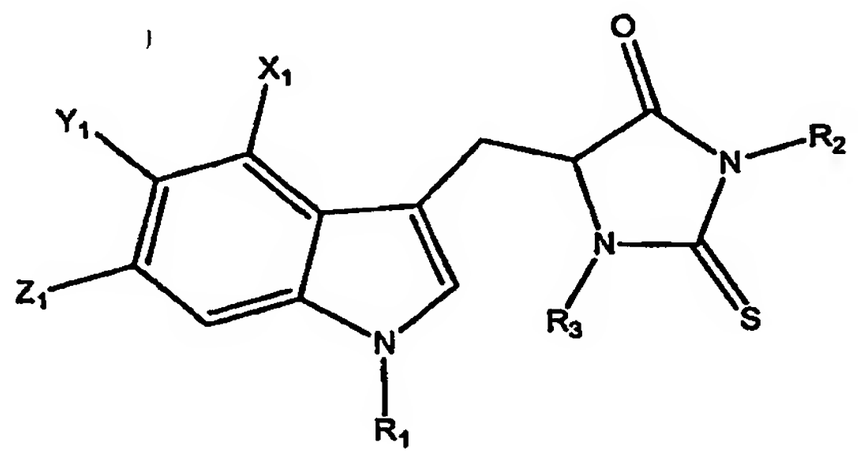
Figure 23 summarizes the findings of the experiments to test the ability of 1MT to cooperate with FTI L-744,832 to cause regression of established tumors in MMTVneu "oncomouse" model. During the two week course of the experiment, an elevation of ~200% in the tumor volume of mock-treated control mice was observed. Treatment of mice with 20 mg/day 1MT, delivered by subcutaneous time-release pellets, retarded but did not block tumor growth. Similarly, treatment of tumor-bearing mice with FTI L-744,832 retarded but did not block tumor growth.

In contrast, the combination of 1MT plus L-744,832 treatment caused tumor regression in the model.

While certain of the preferred embodiments of the present invention have been described and specifically exemplified above, it is not intended that the invention be limited to such embodiments. Various modifications may be made thereto without departing from the scope and spirit of the present invention, as set forth in the following claims.

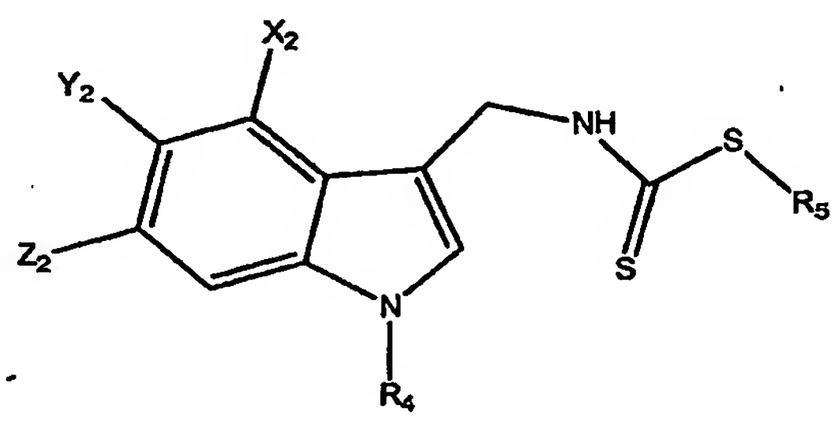
WHAT IS CLAIMED IS:

1. A compound capable of inhibiting indoleamine 2,3-dioxygenase (IDO) activity, said compound has a formula selected from the group consisting of formula (I):



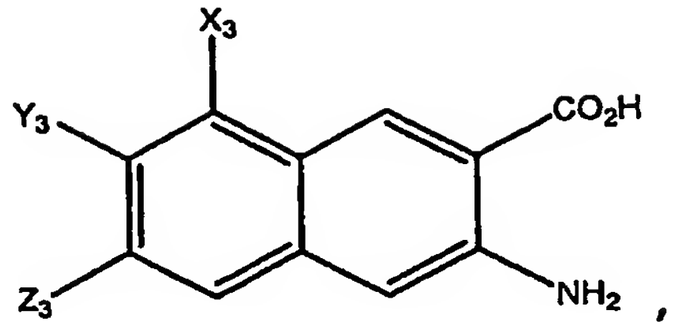
wherein X_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_1 is H or CH_3; R_2 is selected from the group consisting of H, alkyl and aryl; and R_3 is selected from the group consisting of H, alkyl and aryl;

formula (II):



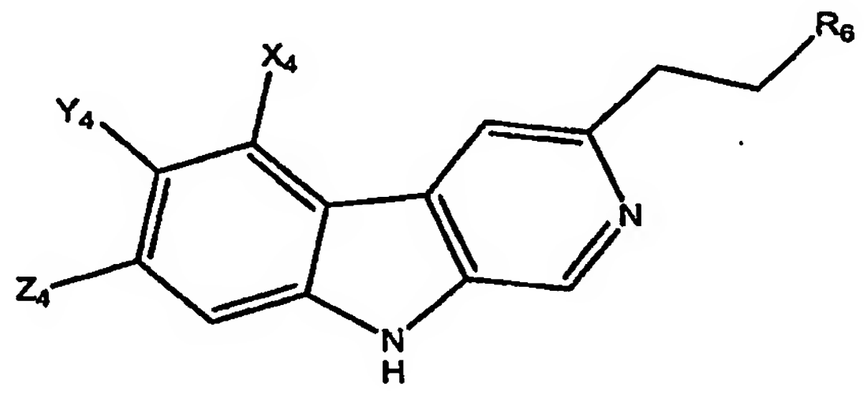
wherein X_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_4 is H or CH_3; and R_5 is selected from the group consisting of H, alkyl and aryl;

formula (III):



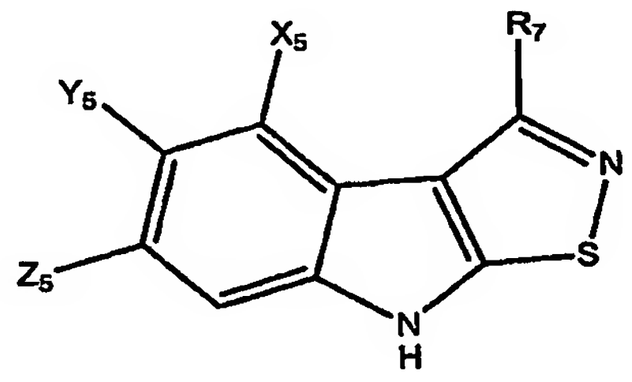
wherein X_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and Z_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl;

formula (IV):



wherein X_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_4 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_6 is alkyl or aryl;

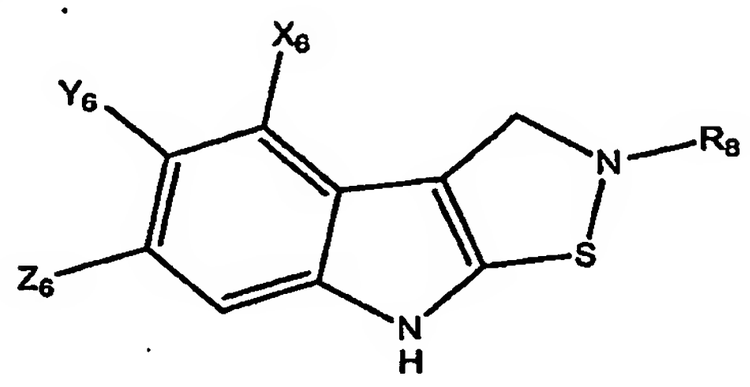
formula (V):



wherein X_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_5 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl,

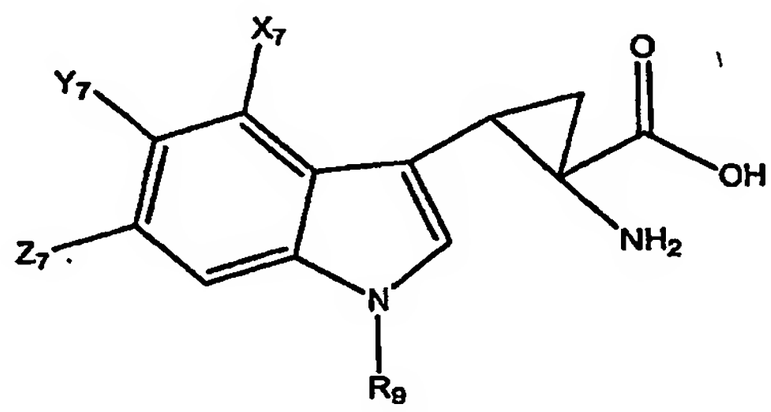
and aryl; Z_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_7 is alkyl or aryl;

formula (VI):



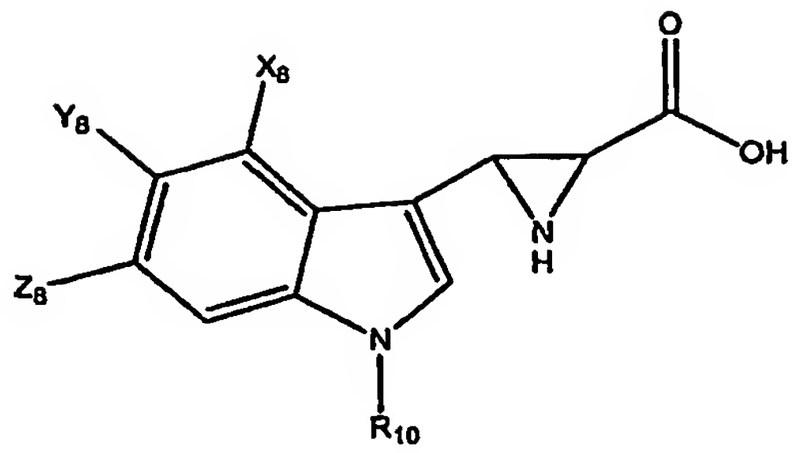
wherein X_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_6 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_8 is alkyl or aryl;

formula (VII):



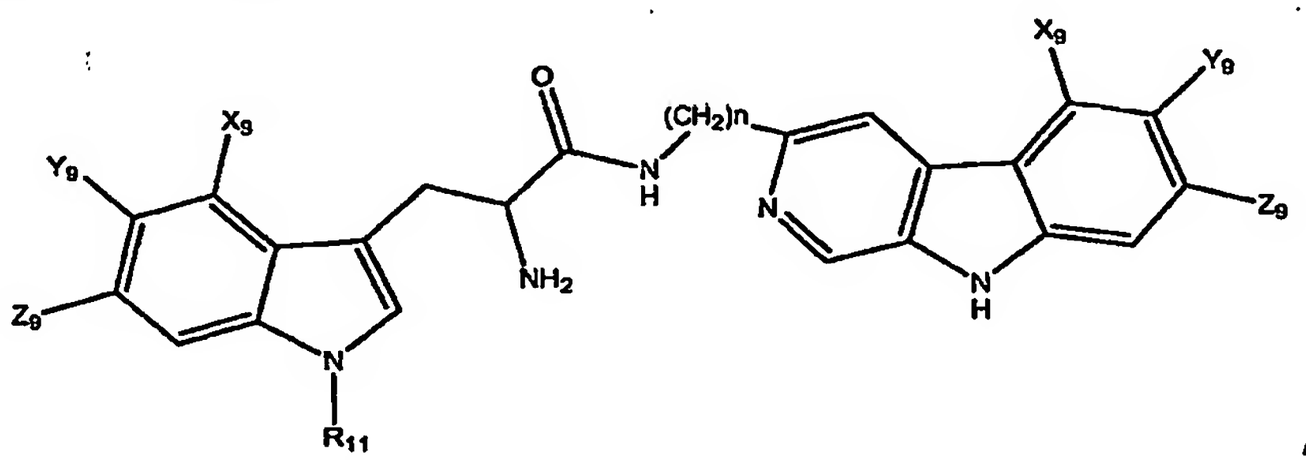
wherein X_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_9 is H or CH_3;

formula (VIII):



wherein X_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{10} is H or CH_3; and

formula (IX):

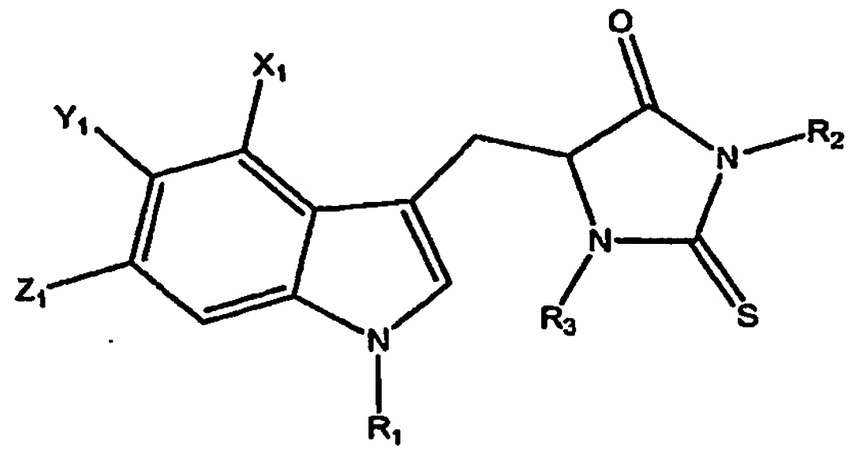


wherein X_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_9 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{11} is H or CH_3.

2. A pharmaceutical composition for the treatment of cancer suitable for administering to a patient in need thereof comprising an effective amount of the compound of claim 1 in a pharmaceutically acceptable carrier medium.

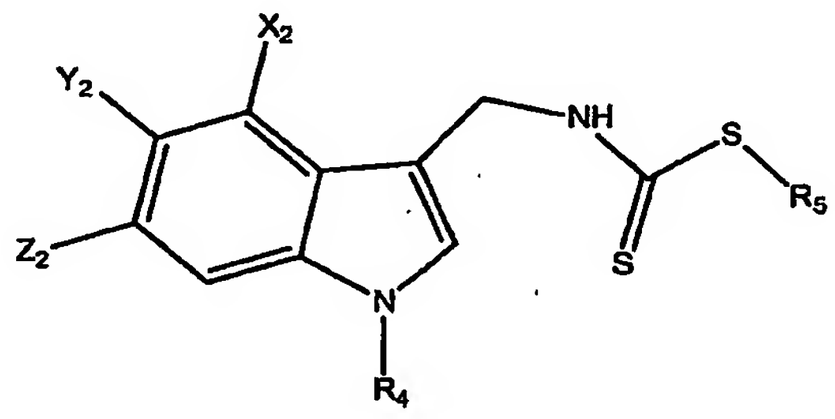
3. A method for treating a cancer in a patient comprising administering of an effective amount of a pharmaceutical composition comprising at least one indoleamine 2,3-dioxygenase (IDO) inhibitor, said at

least one IDO inhibitor is selected from the group of compounds having the formula of formula (I):



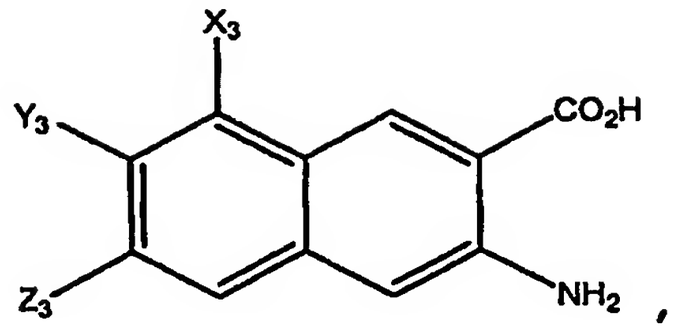
wherein X_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_1 is H or CH_3; R_2 is selected from the group consisting of H, alkyl and aryl; and R_3 is selected from the group consisting of H, alkyl and aryl;

formula (II):



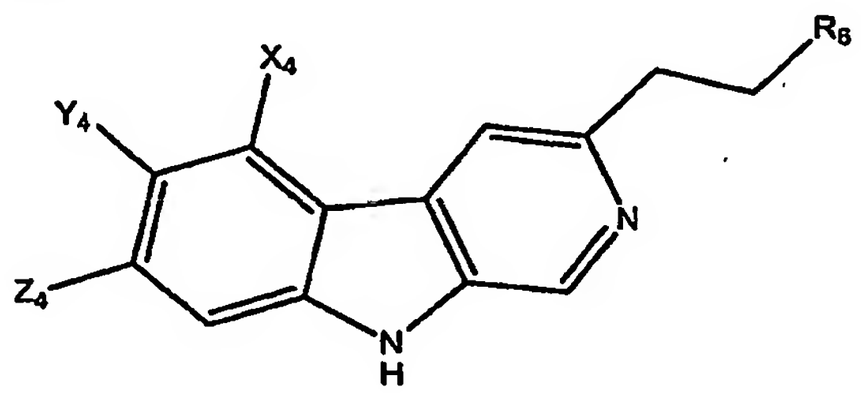
wherein X_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_4 is H or CH_3; and R_5 is selected from the group consisting of H, alkyl and aryl;

formula (III):



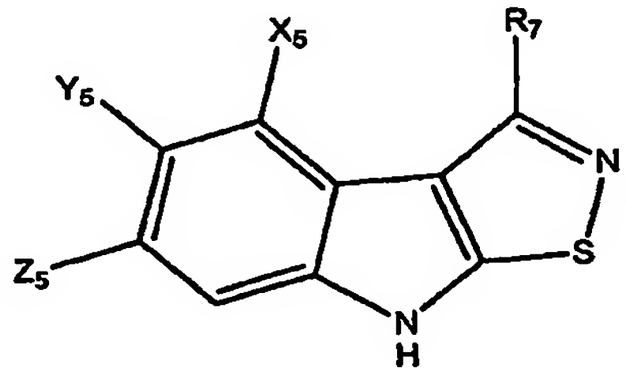
wherein X_3 is selected from the group consisting of H, F, Cl, Br; NO_2, alkyl, and aryl; Y_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and Z_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl;

formula (IV):



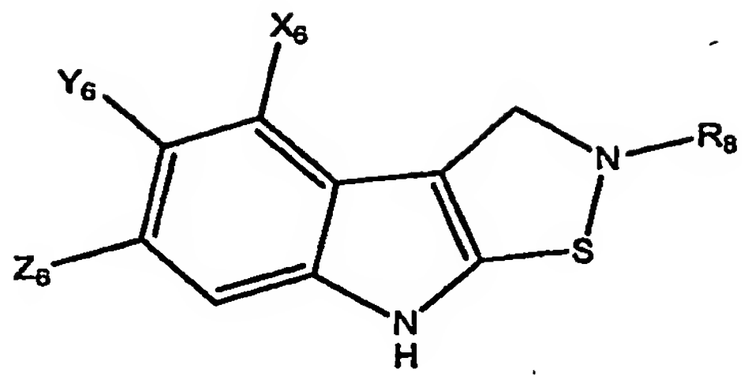
wherein X_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_4 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_6 is alkyl or aryl;

formula (V):



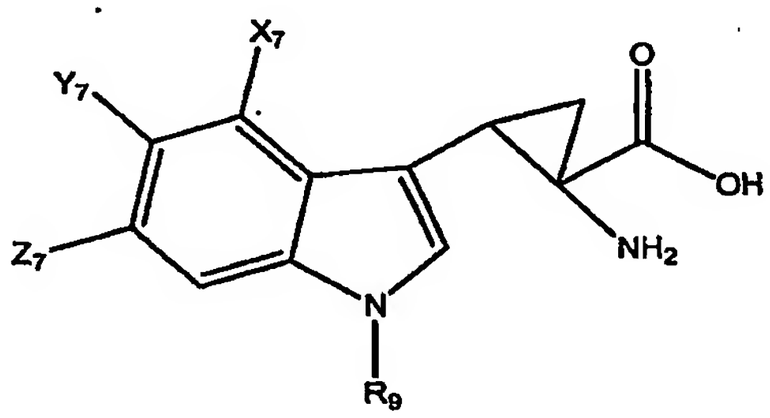
wherein X_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_5 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_7 is alkyl or aryl;

formula (VI):



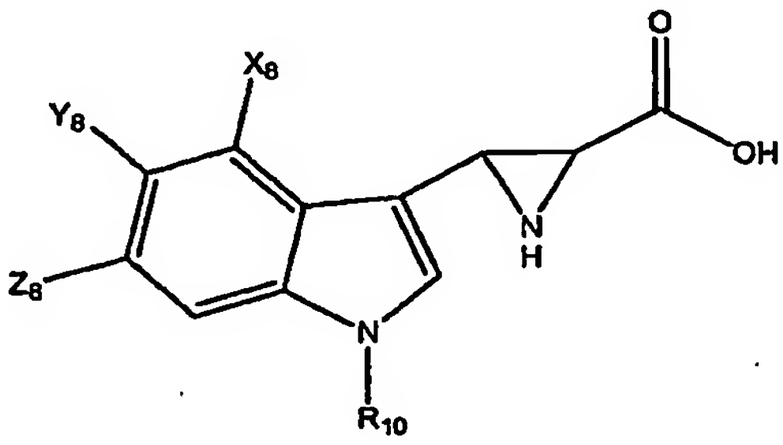
wherein X_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_6 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_8 is alkyl or aryl;

formula (VII):



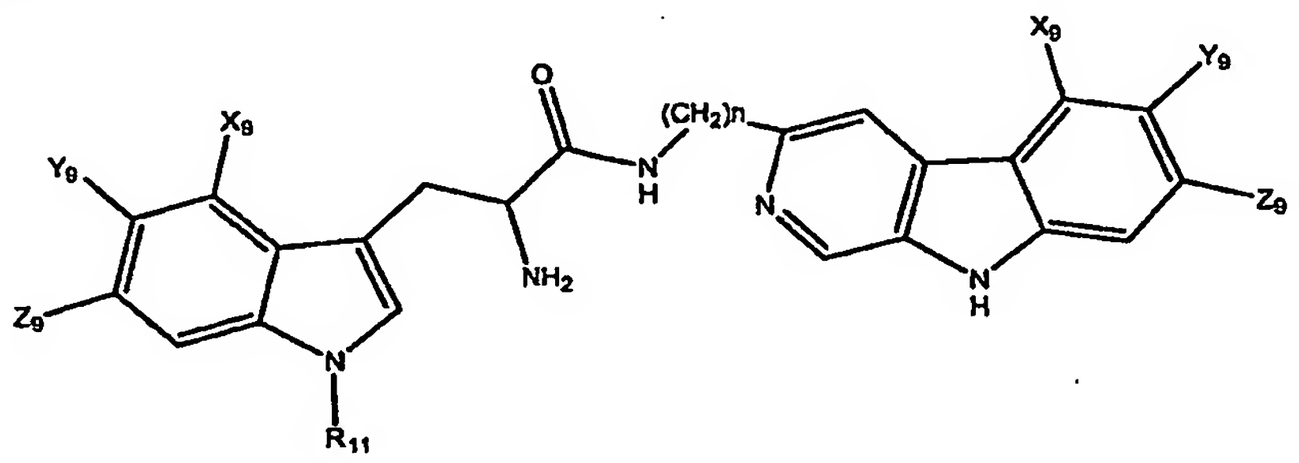
wherein X_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_9 is H or CH_3;

formula (VIII):



wherein X_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{10} is H or CH_3; and

formula (IX):



wherein X_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_9 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{11} is H or CH_3.

4. The method of claim 3, wherein said cancer is selected from the group consisting of cancers of the prostate, colorectum, pancreas, cervix, stomach, endometrium,, brain, liver, bladder, ovary, testis, head, neck, skin (including melanoma and basal carcinoma), mesothelial lining, white blood cell (including lymphoma and leukemia) esophagus, breast, muscle, connective tissue, lung (including small-cell lung carcinoma and non-small-cell carcinoma), adrenal gland, thyroid, kidney, or bone; glioblastoma, mesothelioma, renal cell carcinoma, gastric carcinoma, sarcoma, choriocarcinoma, cutaneous basocellular carcinoma, and testicular seminoma.

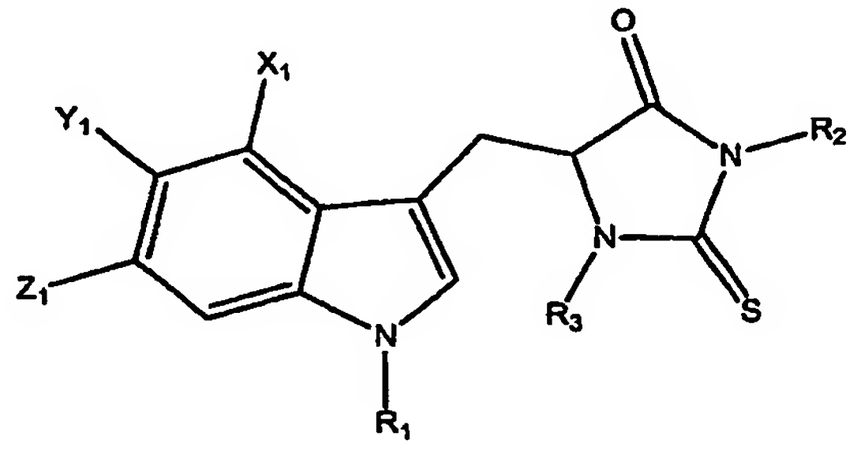
5. A method for treating a cancer in a patient in need thereof comprising administering to said patient, concurrently or sequentially, an effective amount of at least one indoleamine 2,3-dioxygenase (IDO) inhibitor and at least one signal transduction inhibitor (STI).

6. The method of claim 5, wherein said at least one STI is selected from the group consisting of bcr/abl kinase inhibitors, epidermal growth factor (EGF) receptor inhibitors, her-2/neu receptor inhibitors, farnesyl transferase inhibitors (FTIs), inhibitors of Akt family kinases or the Akt pathway, and cell cycle kinase inhibitors.

7. The method of claim 6, wherein said at least one STI is selected from the group consisting of STI 571, SSI-774, C225, ABX-EGF, trastuzumab, L-744,832, rapamycin, LY294002, flavopiridal, and UNC-01.

8. The method of claim 7, wherein said at least one STI is L-744,832.

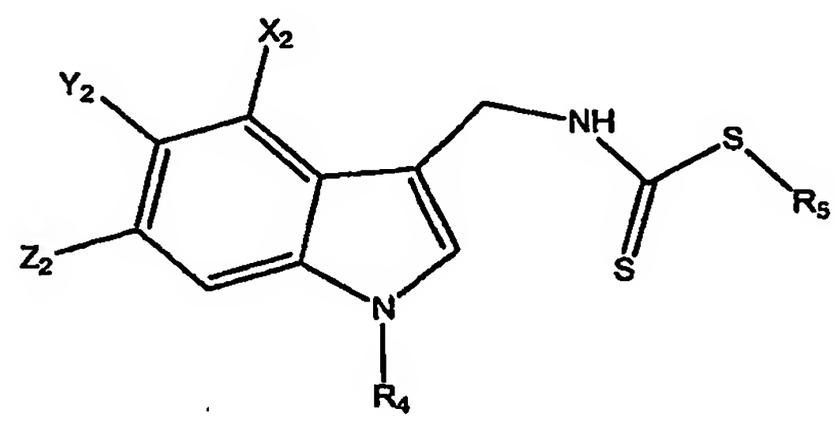
9. The method of claim 5, wherein said at least one IDO inhibitor is selected from the group of compounds having the formula of formula (I):



wherein X_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and

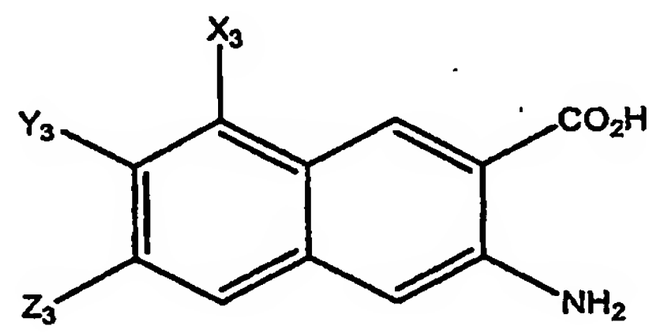
aryl; Z_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_1 is H or CH_3; R_2 is selected from the group consisting of H, alkyl and aryl; and R_3 is selected from the group consisting of H, alkyl and aryl;

formula (II):



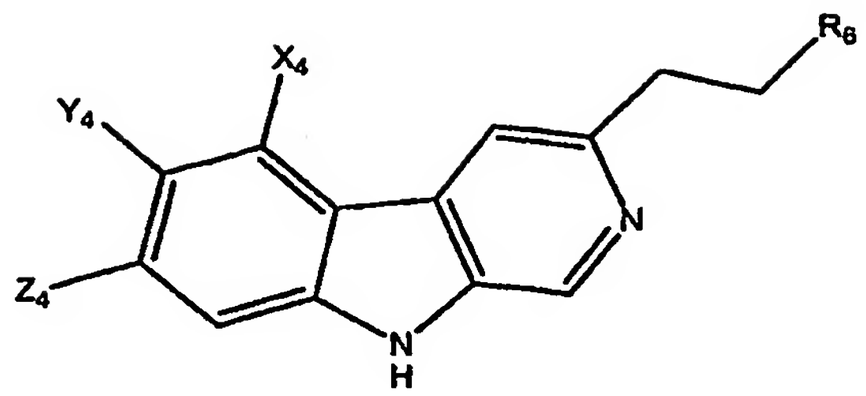
wherein X_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_4 is H or CH_3; and R_5 is selected from the group consisting of H, alkyl and aryl;

formula (III):



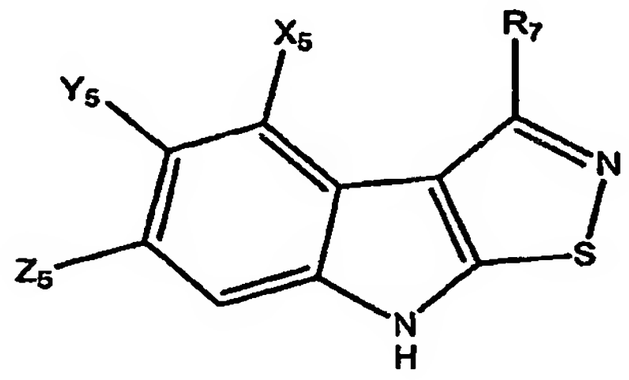
wherein X_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and Z_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl;

formula (IV):



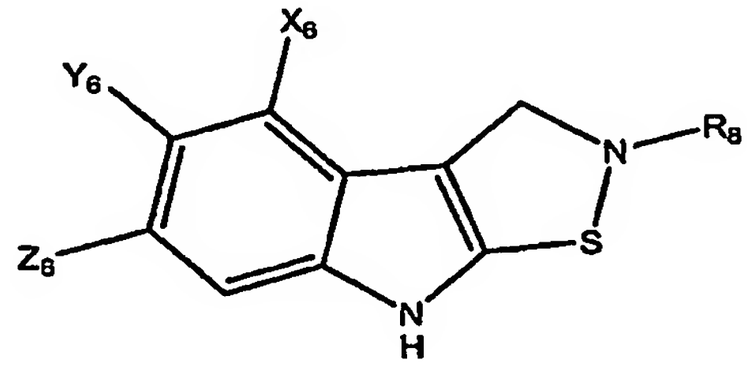
wherein X_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_4 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_6 is alkyl or aryl;

formula (V):



wherein X_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_5 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_7 is alkyl or aryl;

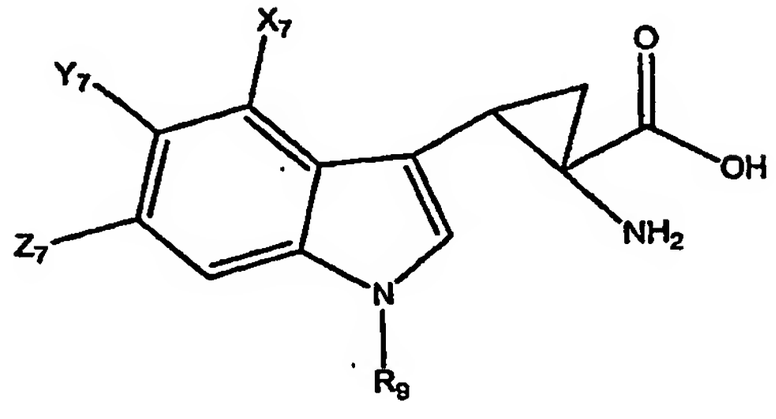
formula (VI):



wherein X_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_6 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl,

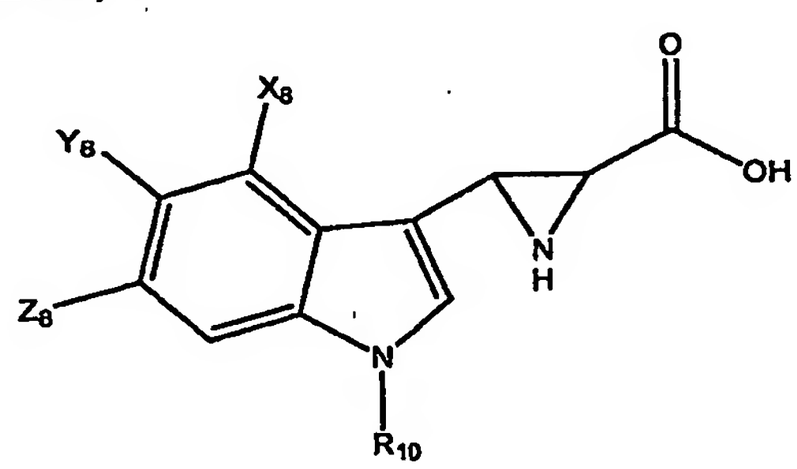
and aryl; Z_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_8 is alkyl or aryl;

formula (VII):



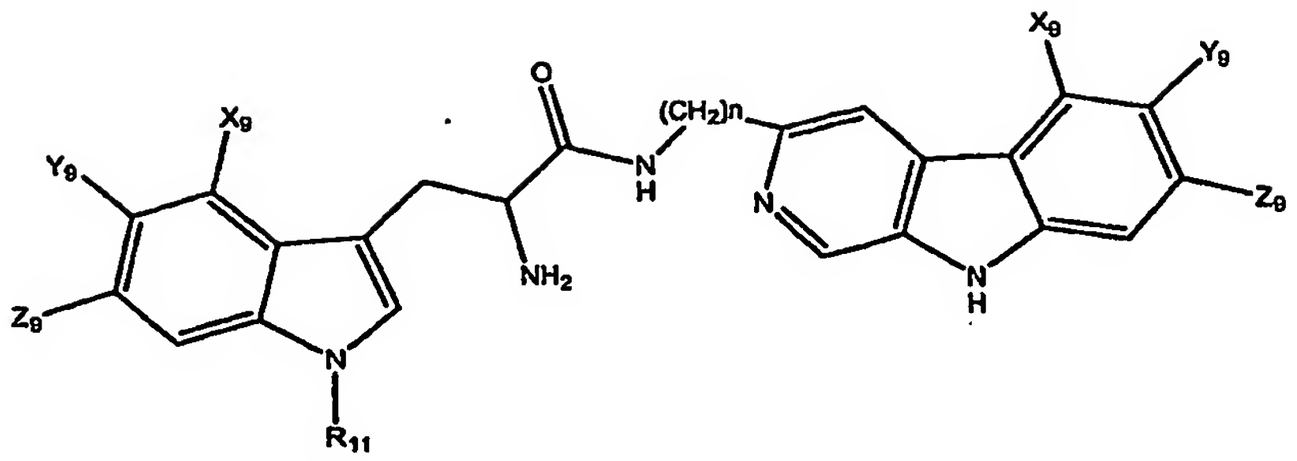
wherein X_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_9 is H or CH_3;

formula (VIII):



wherein X_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{10} is H or CH_3; and

formula (IX):



wherein X_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_9 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{11} is H or CH_3.

10. The method of claim 5, wherein said at least one IDO inhibitor is selected from the group consisting of 1-methyl-DL-tryptophan (1MT), β-(3-benzofuranyl)-DL-alanine, beta-(3-benzo(b)thienyl)-DL-alanine, 6-nitro-L-tryptophan, indole 3-carbinol, 3,3'-diindolylmethane, brassinin, epigallocatechin gallate, 5-Br-4-Cl-indoxyl 1,3-diacetate, 9-vinylcarbazole, acemetacin, 5-bromo-DL-tryptophan, 5-bromoindoxyl diacetate, phenyl-TH-DL-trp, propenyl-TH-DL-trp, and methyl-TH-DL-trp.

11. The method of claim 10, wherein said at least one IDO inhibitor is 1-methyl-tryptophan (1MT).

12. The method of claim 5, wherein said at least one IDO inhibitor and said at least one STI are administered concurrently.

13. The method of claim 5, wherein said at least one IDO inhibitor and said at least one STI are administered sequentially.

14. The method of claim 5, wherein said at least one IDO inhibitor is administered first.

15. The method of claim 5, wherein said at least one STI is administered first.

16. The method of claim 5, wherein said cancer is selected from the group consisting of cancers of the prostate, colorectum, pancreas, cervix, stomach, endometrium,, brain, liver, bladder, ovary, testis, head, neck, skin (including melanoma and basal carcinoma), mesothelial lining, white blood cell (including lymphoma and leukemia) esophagus, breast, muscle, connective tissue, lung (including small-cell lung carcinoma and non-small-cell carcinoma), adrenal gland, thyroid, kidney, or bone; glioblastoma, mesothelioma, renal cell carcinoma, gastric carcinoma, sarcoma, choriocarcinoma, cutaneous basocellular carcinoma, and testicular seminoma.

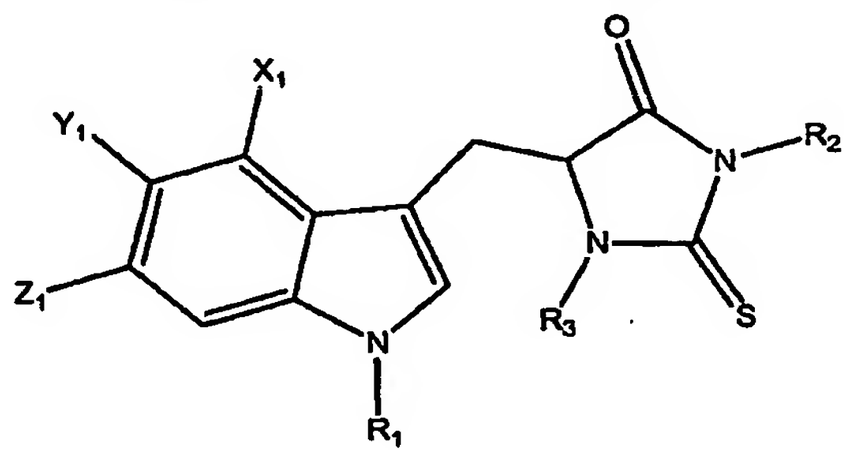
17. A pharmaceutical composition for the treatment of a cancer suitable for administering to a patient in need thereof comprising an effective amount of at least one indoleamine 2,3-dioxygenase (IDO) inhibitor and at least one signal transduction inhibitor (STI) in a pharmaceutically acceptable carrier medium.

18. The pharmaceutical composition of claim 17, wherein said at least one STI is selected from the group consisting of bcr/abl kinase inhibitors, epidermal growth factor (EGF) receptor inhibitors, her-2/neu receptor inhibitors, farnesyl transferase inhibitors (FTIs), inhibitors of Akt family kinases or the Akt pathway, and cell cycle kinase inhibitors.

19. The pharmaceutical composition of claim 18, wherein said at least one STI is selected from the group consisting of STI 571, SSI-774, C225, ABX-EGF, trastuzumab, L-744,832, rapamycin, LY294002, flavopiridal, and UNC-01.

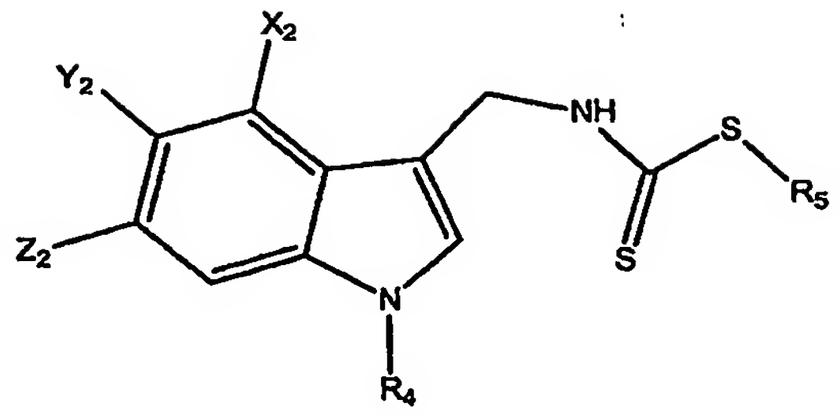
20. The pharmaceutical composition of claim 19, wherein said at least one STI is L-744,832.

21. The pharmaceutical composition of claim 17, wherein said at least one IDO inhibitor is selected from the group of compounds having the formula of formula (I):



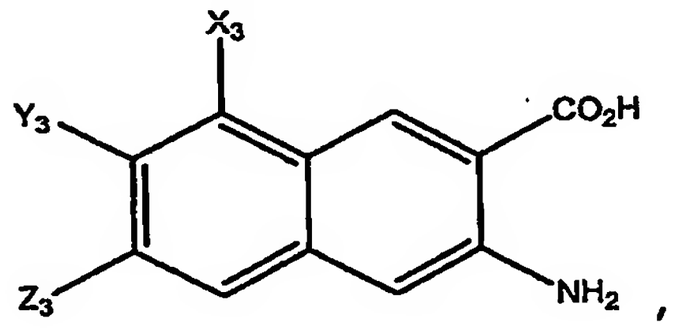
wherein X_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_1 is H or CH_3; R_2 is selected from the group consisting of H, alkyl and aryl; and R_3 is selected from the group consisting of H, alkyl and aryl;

formula (II):



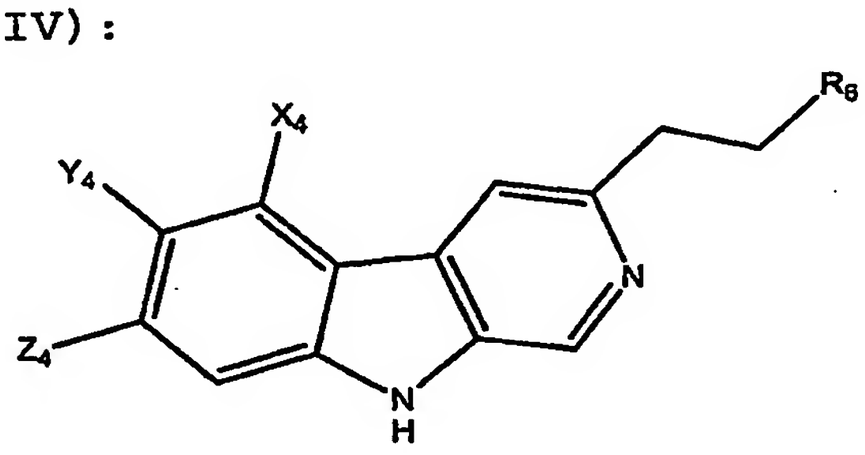
wherein X_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_4 is H or CH_3; and R_5 is selected from the group consisting of H, alkyl and aryl;

formula (III):



wherein X_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and Z_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl;

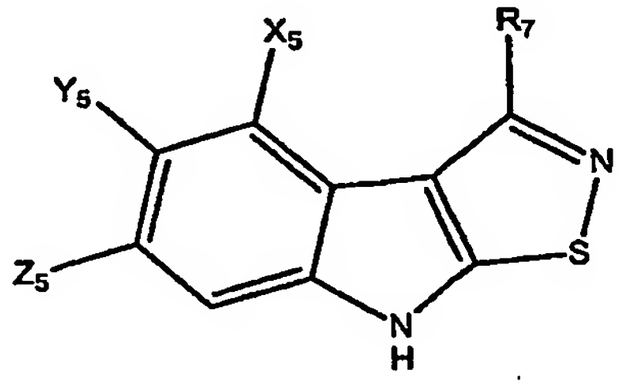
formula (IV):



wherein X_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_4 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl,

and aryl; Z_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_6 is alkyl or aryl;

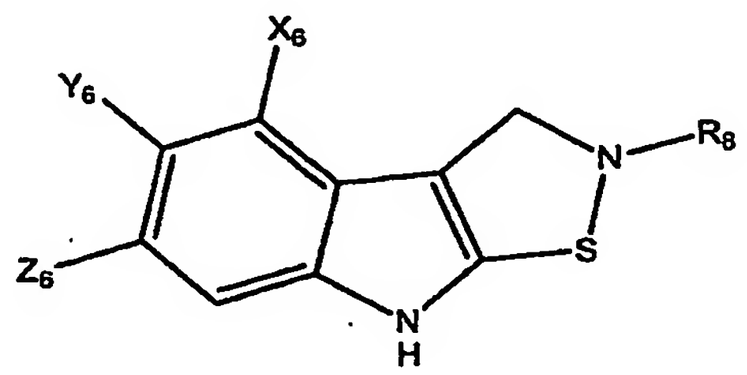
formula (V):



,

wherein X_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_5 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_7 is alkyl or aryl;

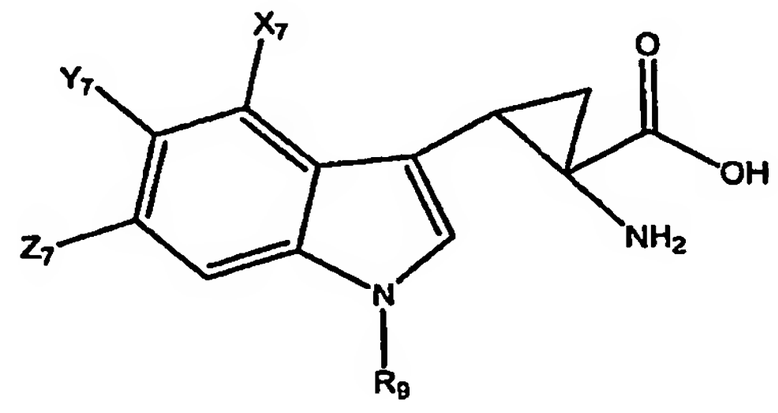
formula (VI):



,

wherein X_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_6 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_8 is alkyl or aryl;

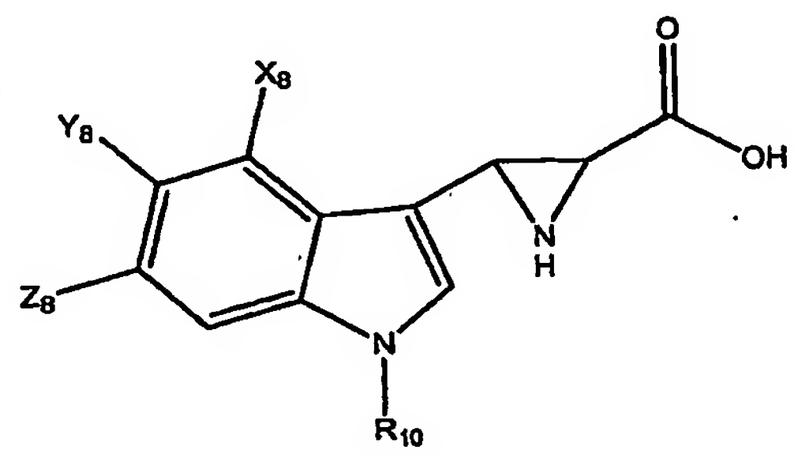
formula (VII):



,

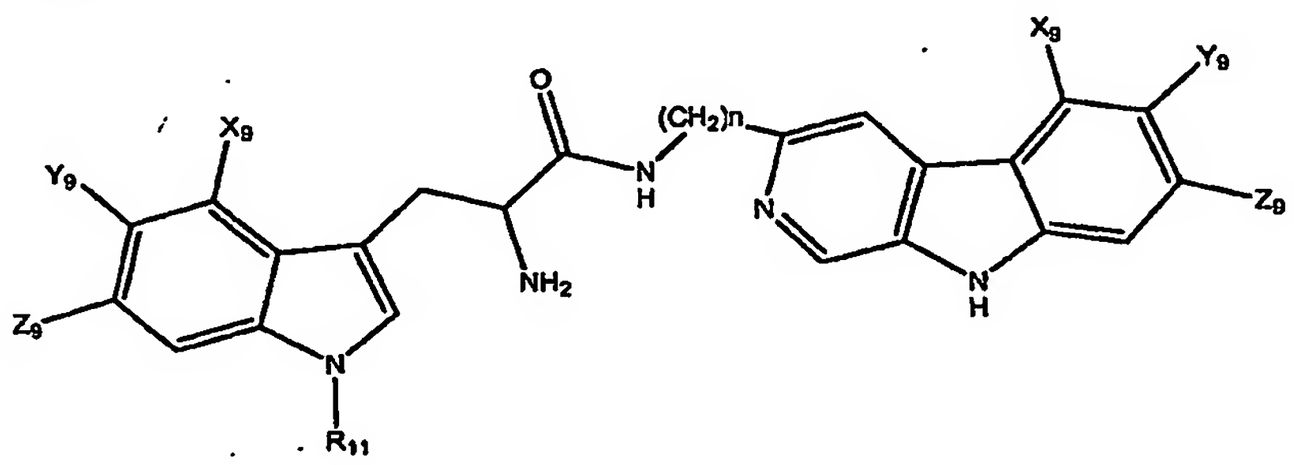
wherein X_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_9 is H or CH_3;

formula (VIII):



wherein X_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{10} is H or CH_3; and

formula (IX):



wherein X_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_9 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{11} is H or CH_3.

22. The pharmaceutical composition of claim 17, wherein said at least one inhibitor of IDO is selected

from the group consisting of 1-methyl-DL-tryptophan (1MT), β-(3-benzofuranyl)-DL-alanine, beta-(3-benzo(b)thienyl)-DL-alanine, 6-nitro-L-tryptophan, indole 3-carbinol, 3,3'-diindolylmethane, brassinin, epigallocatechin gallate, 5-Br-4-Cl-indoxyl 1,3-diacetate, 9-vinylcarbazole, acemetacin, 5-bromo-DL-tryptophan, 5-bromoindoxyl diacetate, phenyl-TH-DL-trp, propenyl-TH-DL-trp, and methyl-TH-DL-trp.

23. The pharmaceutical composition of claim 22, wherein said at least one IDO inhibitor is 1-methyl-tryptophan (1MT).

24. A method for treating a cancer in a patient in need thereof comprising administering to said patient, concurrently or sequentially, an effective amount of at least one immunomodulator other than IDO inhibitors and an effective amount of at least one cytotoxic chemotherapeutic agent or at least one STI.

25. The method of claim 24, wherein said at least one immunomodulator is selected from the group consisting of CD40L, B7, B7RP1, ant-CD40, anti-CD38, anti-ICOS, 4-IBB ligand, dendritic cell cancer vaccine, IL2, IL12, IL1, IL18, ELC/CCL19, SLC/CCL21, MCP-1, IL-4, IL-18, TNF, IL-15, MDC, IFNa/b, M-CSF, IL-3, GM-CSF, IL-13, anti-IL-10, bacterial lipopolysaccharide (LPS), and poly CpG DNA.

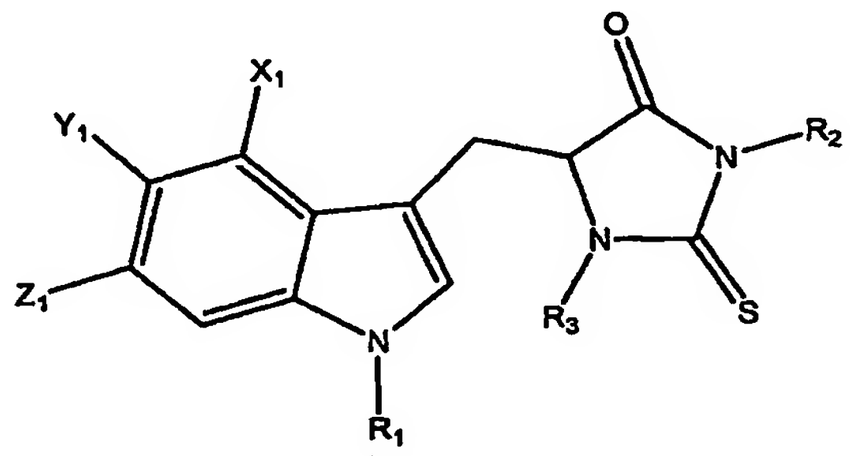
26. The method of claim 24, wherein said at least one cytotoxic chemotherapeutic agent is selected from the group consisting of placitaxel (Taxol®), cisplatin, docetaxol, carboplatin, vincristine, vinblastine, methotrexate, cyclophosphamide, CPT-11, 5-fluorouracil (5-FU), gemcitabine, estramustine, carmustine, adriamycin

(doxorubicin), etoposide, arsenic trioxide, irinotecan, and epothilone derivatives.

27. The method of claim 24, wherein said at least one STI is selected from the group consisting of STI 571, SSI-774, C225, ABX-EGF, trastuzumab, L-744,832, rapamycin, LY294002, flavopiridal, and UNC-01.

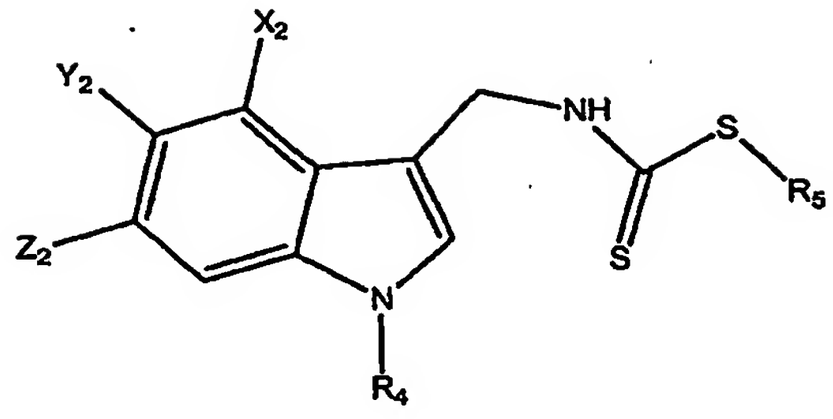
28. A method for treating a chronic viral infection in a patient in need thereof comprising administering to said patient, concurrently or sequentially, an effective amount of at least one indoleamine 2,3-dioxygenase (IDO) inhibitor and at least one chemotherapeutic agent.

29. The method of claim 28, wherein said at least one IDO inhibitor is selected from the group of compounds having the formula of formula (I):



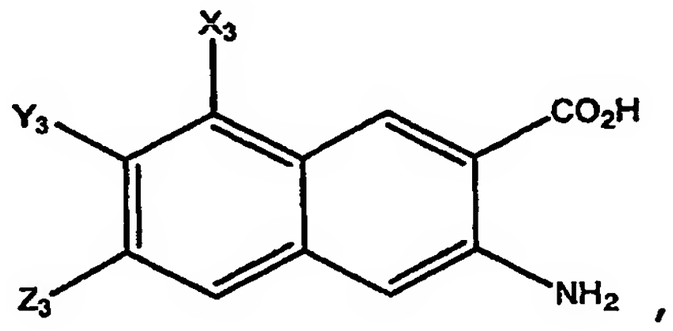
wherein X_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_1 is H or CH_3; R_2 is selected from the group consisting of H, alkyl and aryl; and R_3 is selected from the group consisting of H, alkyl and aryl;

formula (II):



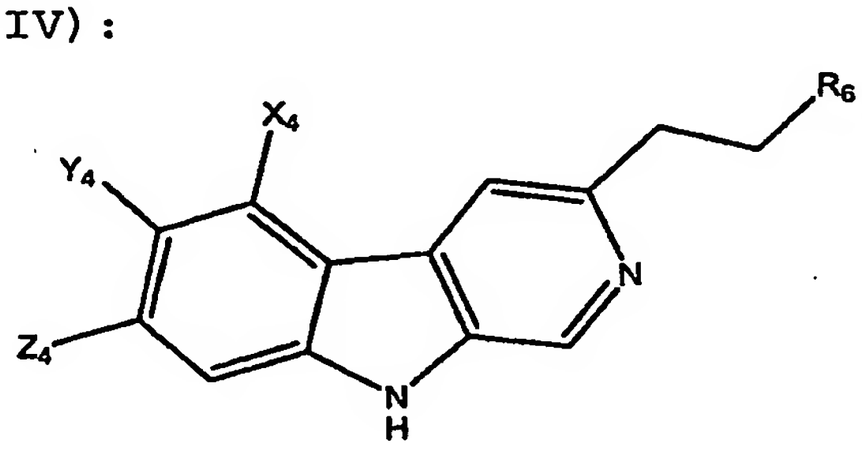
wherein X_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_4 is H or CH_3; and R_5 is selected from the group consisting of H, alkyl and aryl;

formula (III):



wherein X_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and Z_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl;

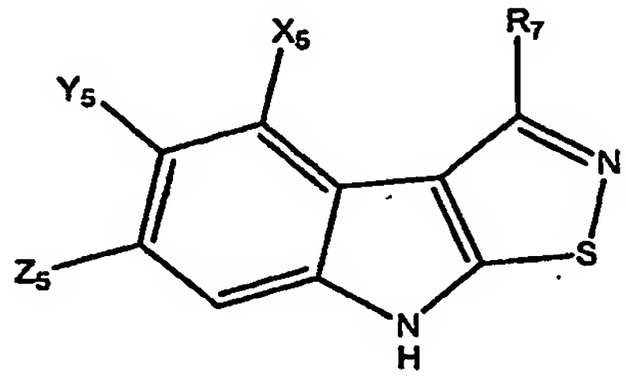
formula (IV):



wherein X_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_4 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl,

and aryl; Z_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_6 is alkyl or aryl;

formula (V):



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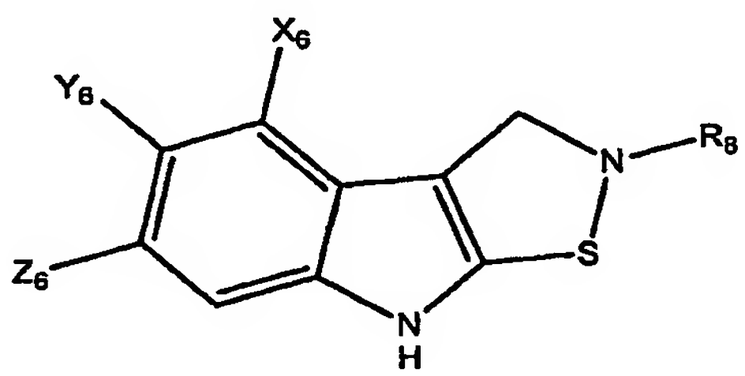
wherein X_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_5 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_7 is alkyl or aryl;

formula (VI):



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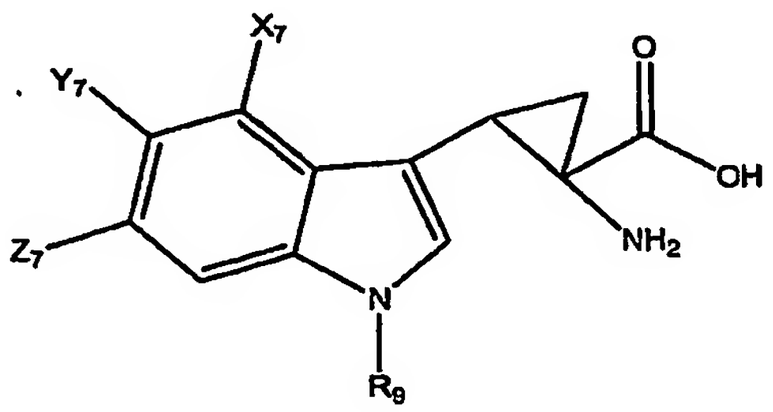
wherein X_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_6 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_8 is alkyl or aryl;

formula (VII):



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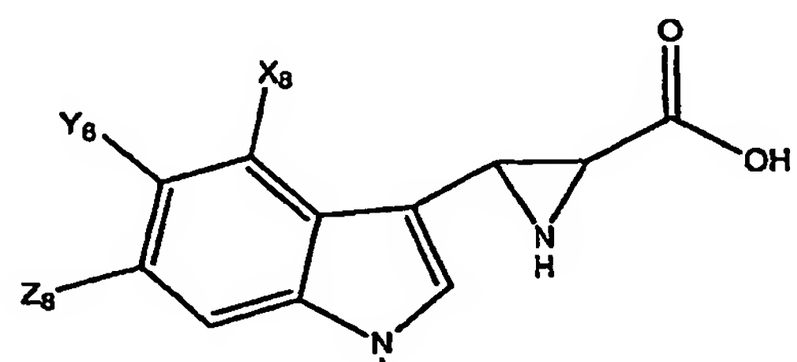
wherein X_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_9 is H or CH_3;

formula (VIII):



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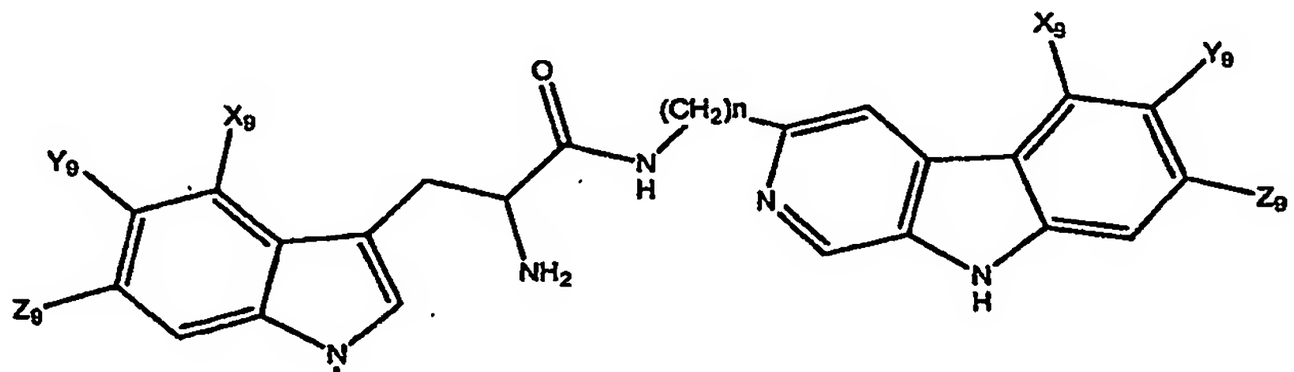
wherein X_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{10} is H or CH_3; and

formula (IX):



,

wherein X_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_9 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{11} is H or CH_3.

30. The method of claim 28, wherein said at least one IDO inhibitor is selected from the group consisting

of 1-methyl-DL-tryptophan (1MT), β-(3-benzofuranyl)-DL-alanine, beta-(3-benzo(b)thienyl)-DL-alanine, 6-nitro-L-tryptophan, indole 3-carbinol, 3,3'-diindolylmethane, brassinin, epigallocatechin gallate, 5-Br-4-Cl-indoxyl 1,3-diacetate, 9-vinylcarbazole, acemetacin, 5-bromo-DL-tryptophan, 5-bromoindoxyl diacetate, phenyl-TH-DL-trp, propenyl-TH-DL-trp, and methyl-TH-DL-trp.

31. The method of claim 28, wherein said at least one IDO inhibitor is 1-methyl-tryptophan (1MT).

32. The method of claim 28, wherein said at least one chemotherapeutic agent is selected from the group consisting of placitaxel (Taxol®), cisplatin, docetaxol, carboplatin, vincristine, vinblastine, methotrexate, cyclophosphamide, CPT-11, 5-fluorouracil (5-FU), gemcitabine, estramustine, carmustine, adriamycin (doxorubicin), etoposide, arsenic trioxide, irinotecan, and epothilone derivatives.

33. The method of claim 28, wherein said at least one IDO inhibitor and said at least one chemotherapeutic agent are administered concurrently.

34. The method of claim 28, wherein said at least one IDO inhibitor and said at least one chemotherapeutic agent are administered sequentially.

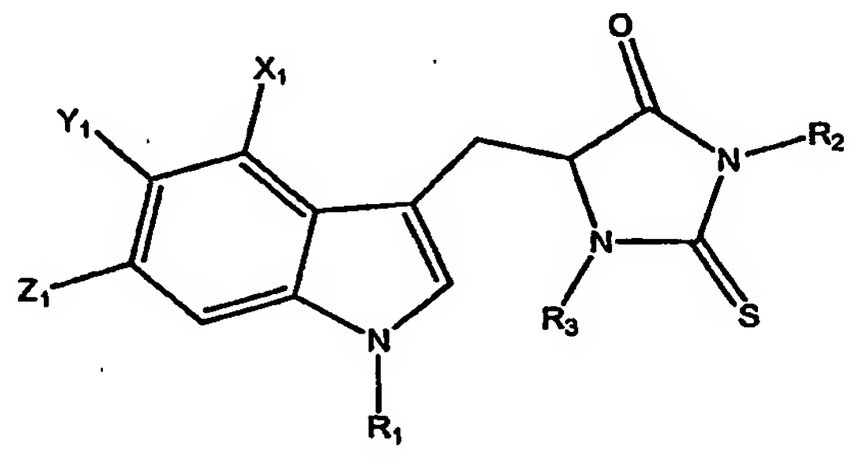
35. The method of claim 34, wherein said at least one IDO inhibitor is administered first.

36. The method of claim 34, wherein said at least one chemotherapeutic agent is administered first.

37. The method of claim 28, wherein said chronic viral infection is selected from the group consisting of: hepatitis C virus (HCV), human papilloma virus (HPV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus, coxsackie virus, human immunodeficiency virus (HIV).

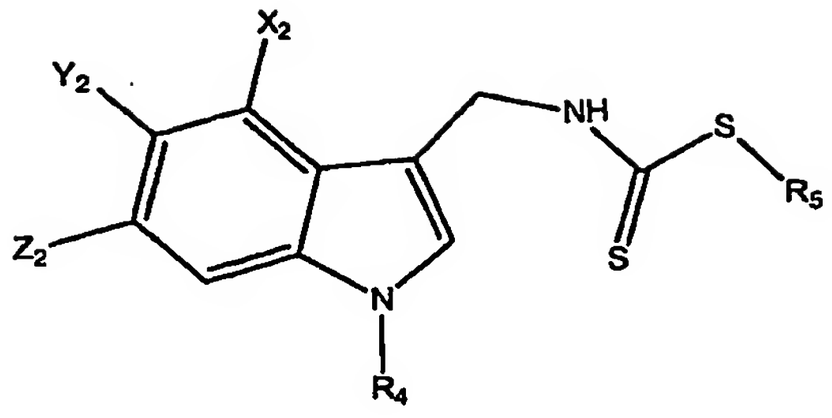
38. A pharmaceutical composition for the treatment of a chronic viral infection suitable for administering to a patient in need thereof comprising an effective amount of at least one indoleamine 2,3-dioxygenase (IDO) inhibitor and at least one chemotherapeutic agent in a pharmaceutically acceptable carrier medium.

39. The pharmaceutical composition of claim 38, wherein said at least one IDO inhibitor is selected from the group of compounds having the formula of formula (I):



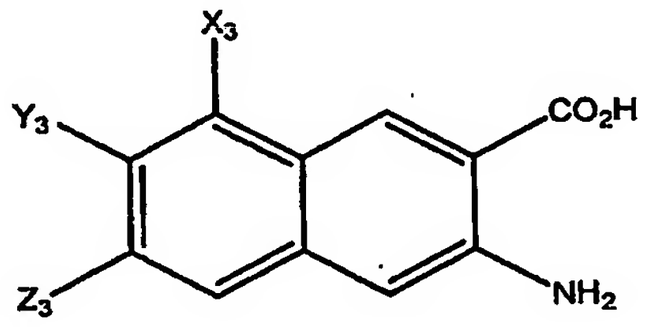
wherein X_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_1 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_1 is H or CH_3; R_2 is selected from the group consisting of H, alkyl and aryl; and R_3 is selected from the group consisting of H, alkyl and aryl;

formula (II):



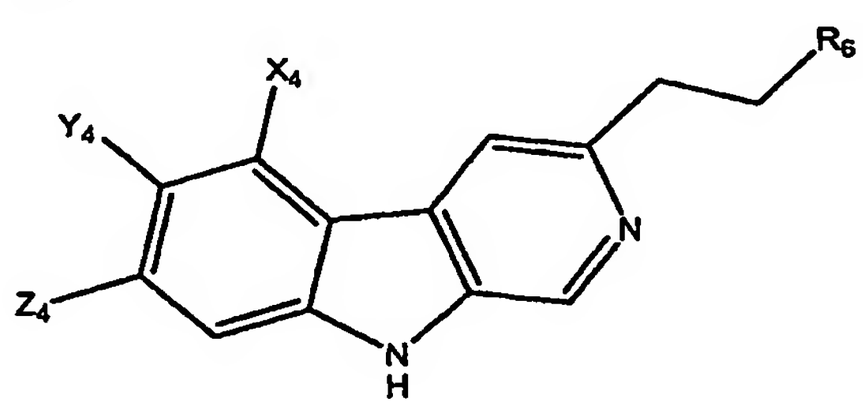
wherein X_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_2 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; R_4 is H or CH_3; and R_5 is selected from the group consisting of H, alkyl and aryl;

formula (III):



wherein X_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and Z_3 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl;

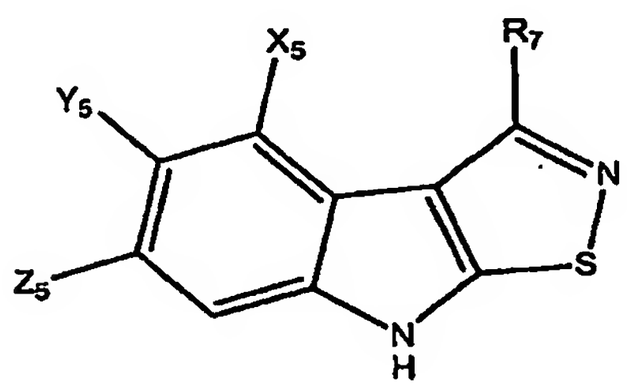
formula (IV):



wherein X_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_4 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl,

and aryl; Z_4 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_6 is alkyl or aryl;

formula (V):



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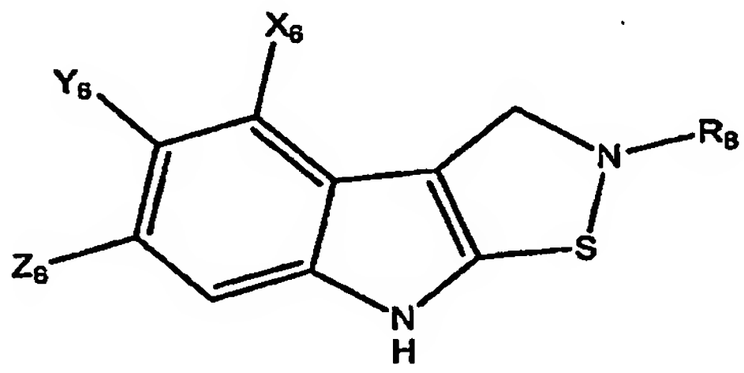
wherein X_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_5 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_5 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_7 is alkyl or aryl;

formula (VI):



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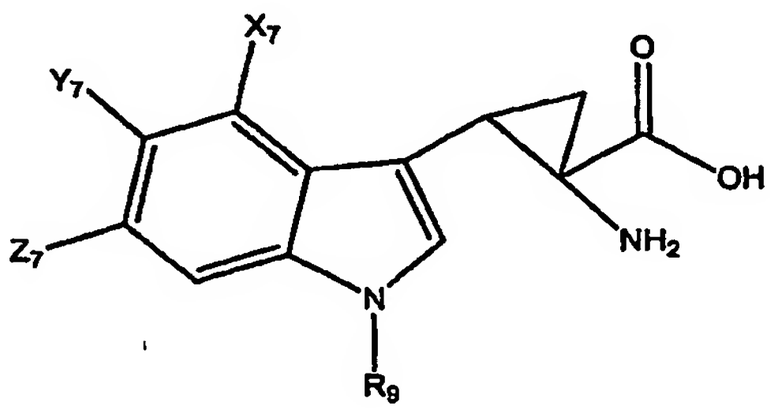
wherein X_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_6 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_6 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_8 is alkyl or aryl;

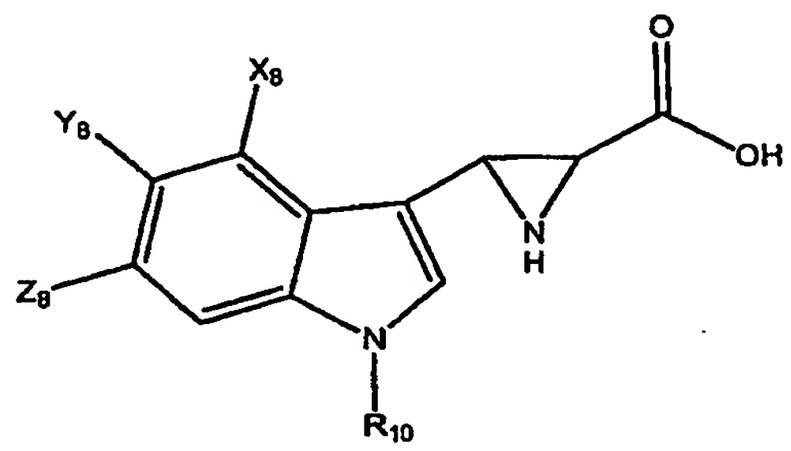
formula (VII):



,

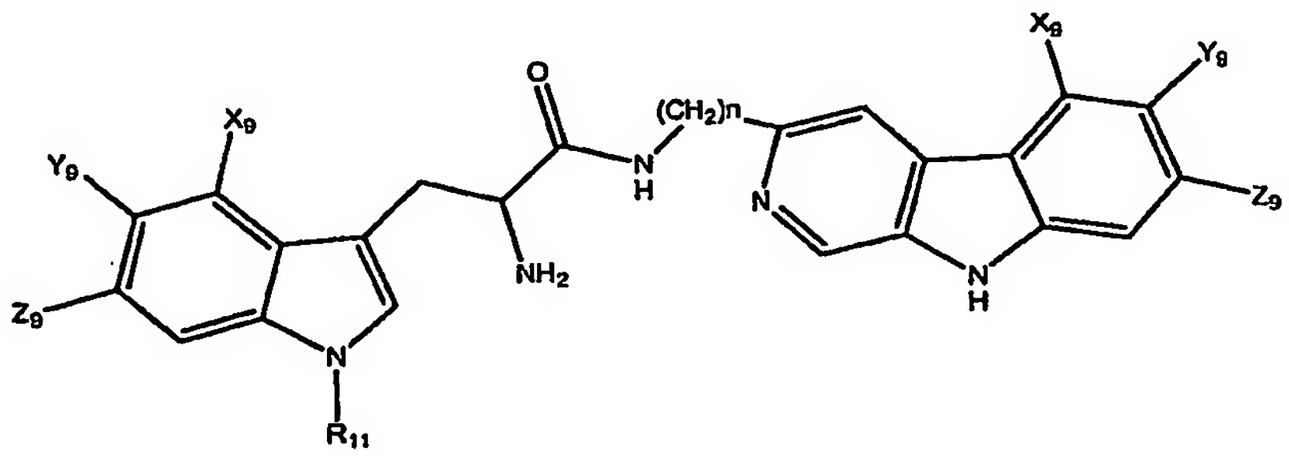
wherein X_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_7 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_9 is H or CH_3;

formula (VIII):



wherein X_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Z_8 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{10} is H or CH_3; and

formula (IX):



wherein X_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; Y_9 is selected from the group consisting of H, F, Cl, Br, NO_2, N=C=S, alkyl, and aryl; Z_9 is selected from the group consisting of H, F, Cl, Br, NO_2, alkyl, and aryl; and R_{11} is H or CH_3.

40. The pharmaceutical composition of claim 38, wherein said at least one inhibitor of IDO is selected

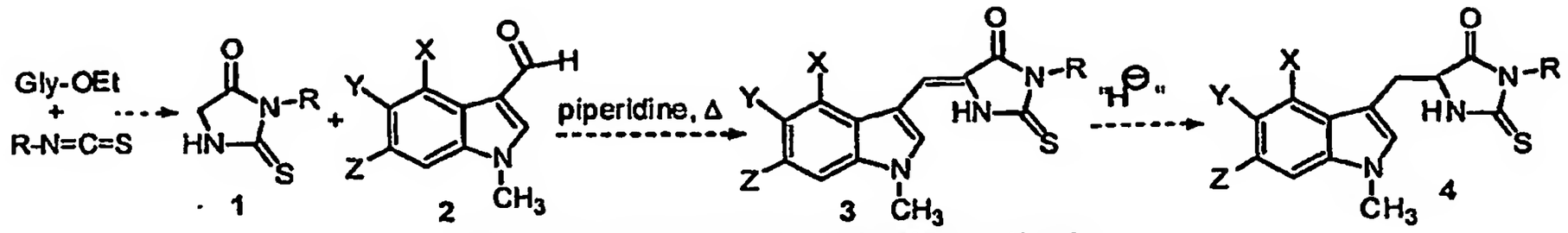
from the group consisting of 1-methyl-DL-tryptophan (1MT), β-(3-benzofuranyl)-DL-alanine, beta-(3-benzo(b)thienyl)-DL-alanine, 6-nitro-L-tryptophan, indole 3-carbinol, 3,3'-diindolylmethane, brassinin, epigallocatechin gallate, 5-Br-4-Cl-indoxyl 1,3-diacetate, 9-vinylcarbazole, acemetacin, 5-bromo-DL-tryptophan, 5-bromoindoxyl diacetate, phenyl-TH-DL-trp, propenyl-TH-DL-trp, and methyl-TH-DL-trp.

41. The pharmaceutical composition of claim 38, wherein said at least one IDO inhibitor is 1-methyl-tryptophan (1MT).

42. The method of claim 38, wherein said at least one chemotherapeutic agent is selected from the group consisting of placitaxel (Taxol®), cisplatin, docetaxol, carboplatin, vincristine, vinblastine, methotrexate, cyclophosphamide, CPT-11, 5-fluorouracil (5-FU), gemcitabine, estramustine, carmustine, adriamycin (doxorubicin), etoposide, arsenic trioxide, irinotecan, and epothilone derivatives.

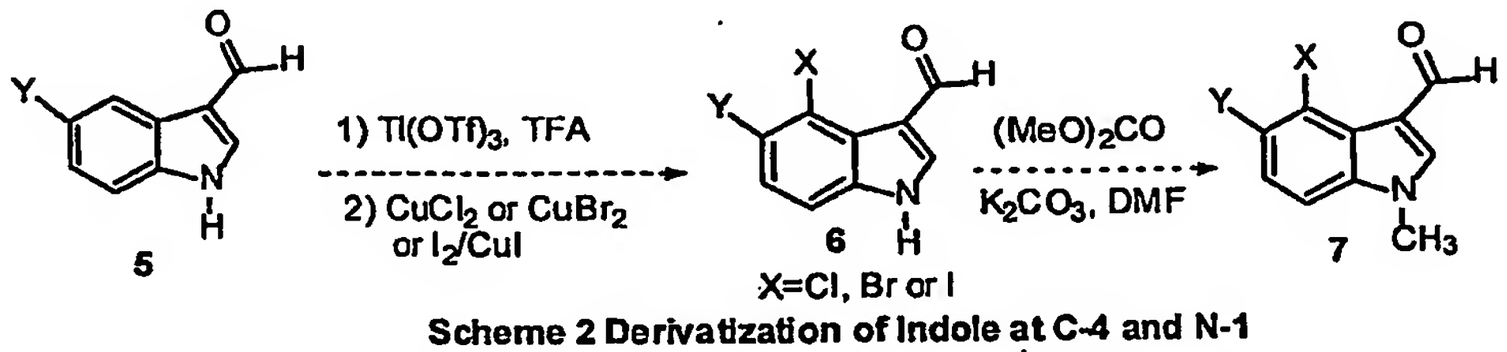
ABSTRACT

Compositions and methods are provided for the treatment of malignancy.



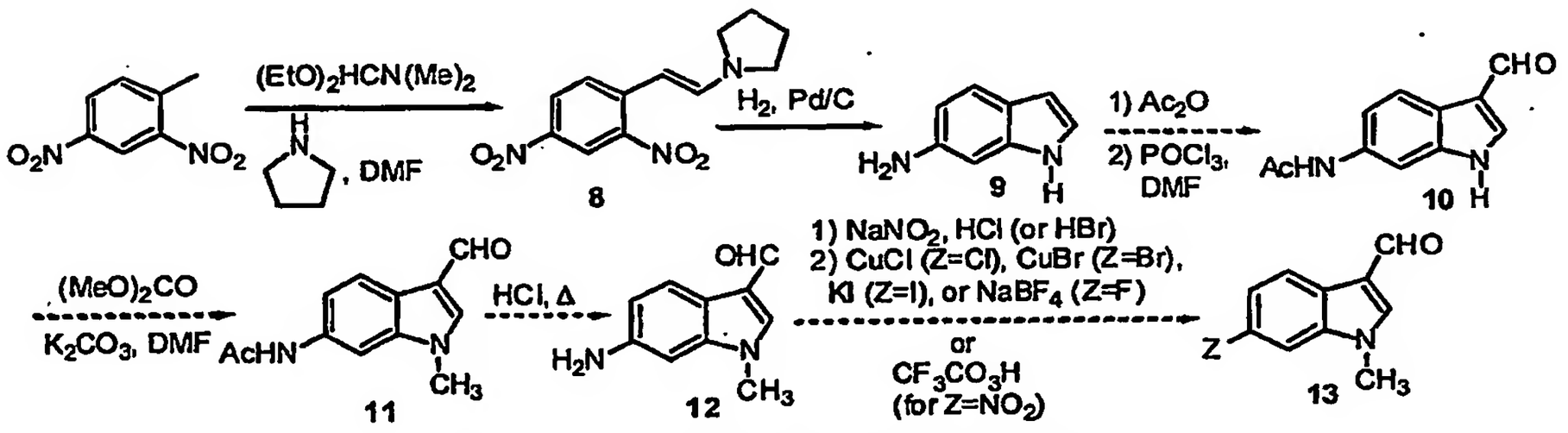
Scheme 1 Thiohydantoin derivative synthesis

Figure 1



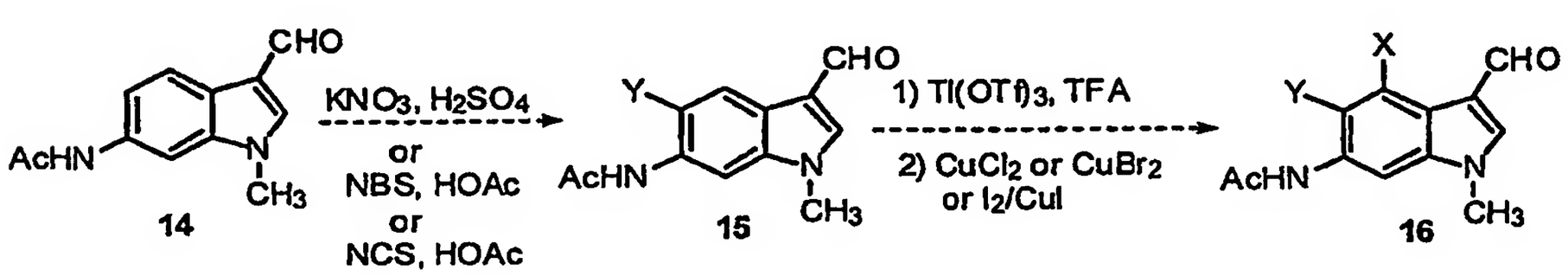
Scheme 2 Derivatization of Indole at C-4 and N-1

Figure 2



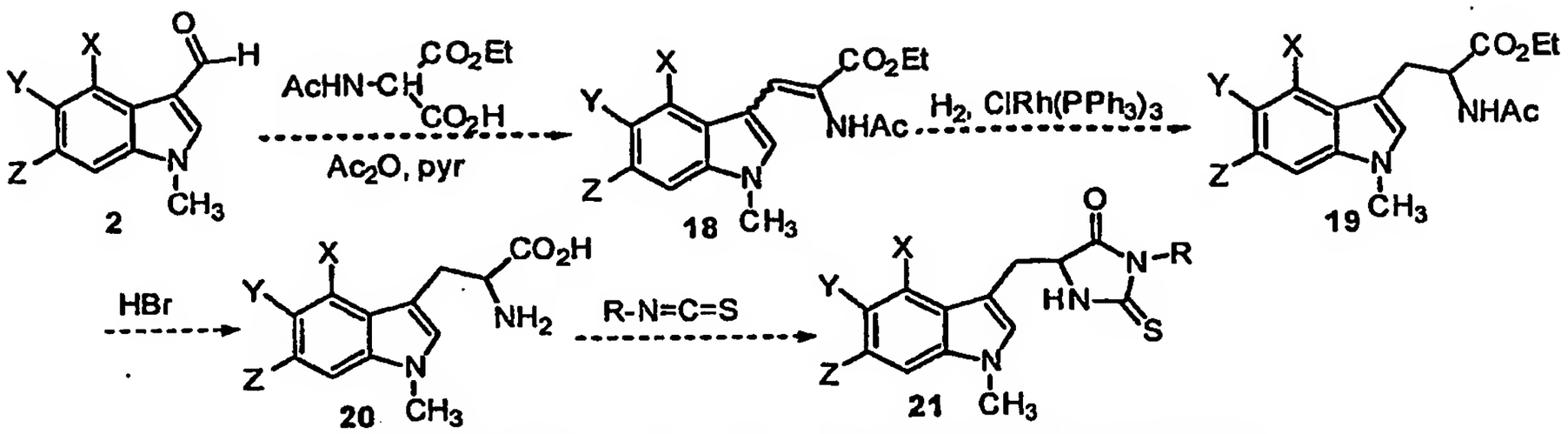
Scheme 3 Synthesis of C-6 Substituted Indoles

Figure 3



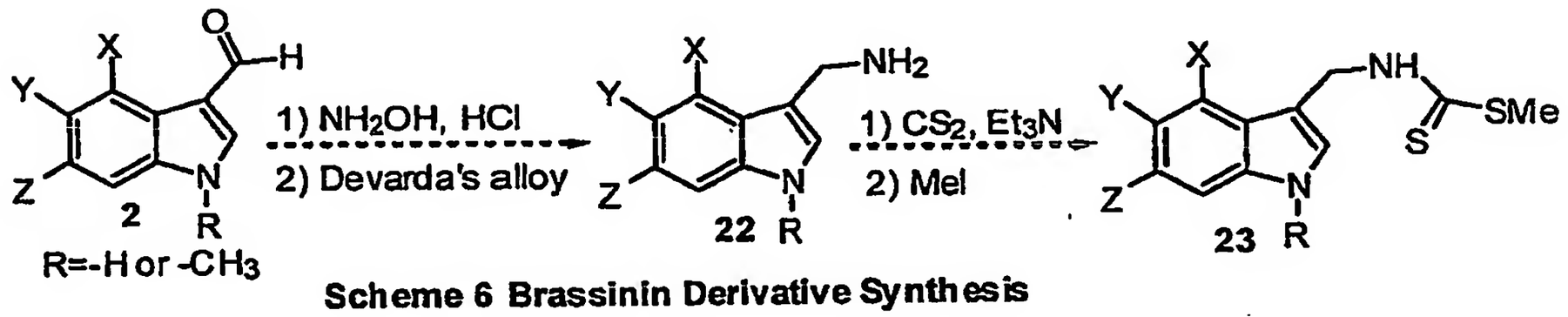
Scheme 4 Synthesis of C-4, C-5 and C-6 Trisubstituted Indoles

Figure 4



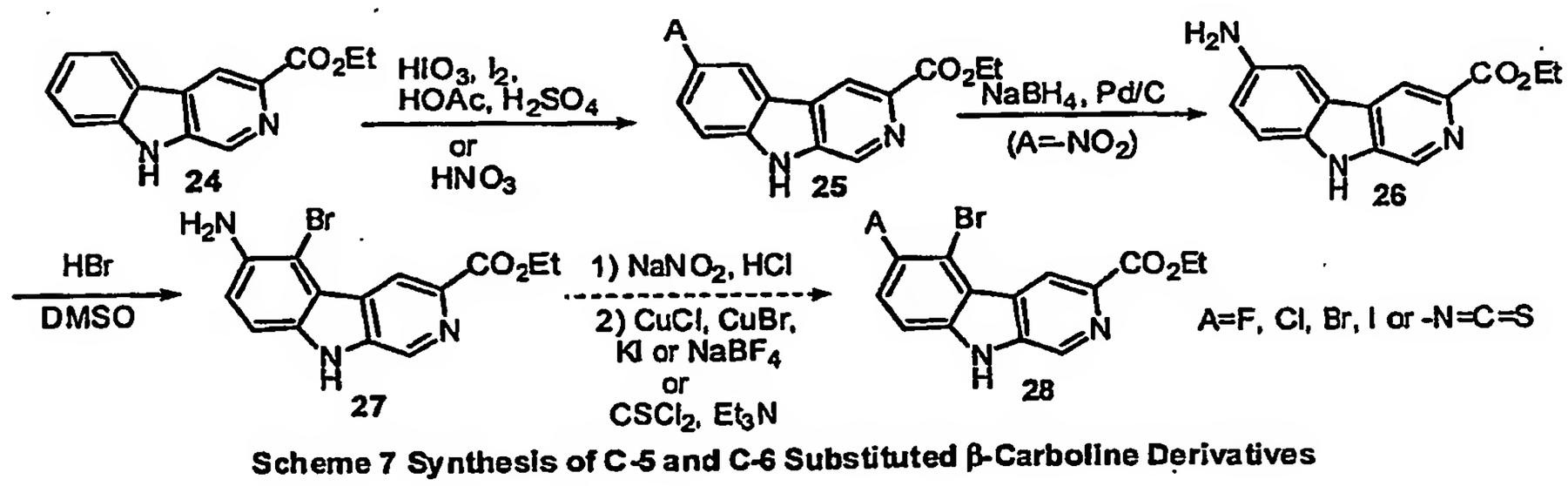
Scheme 5 Alternative Synthesis of Thiohydantoin Derivatives

Figure 5



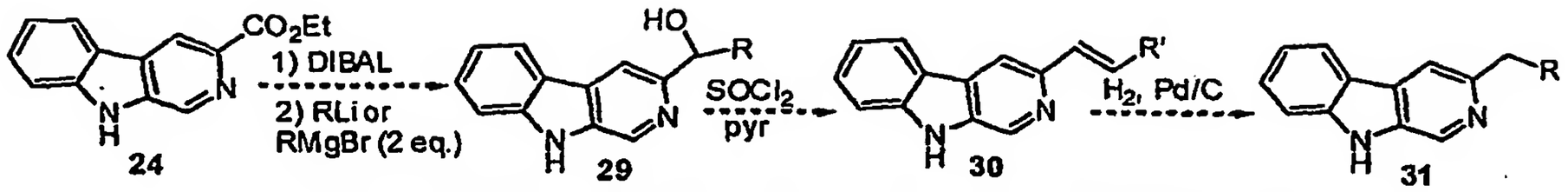
Scheme 6 Brassinin Derivative Synthesis

Figure 6



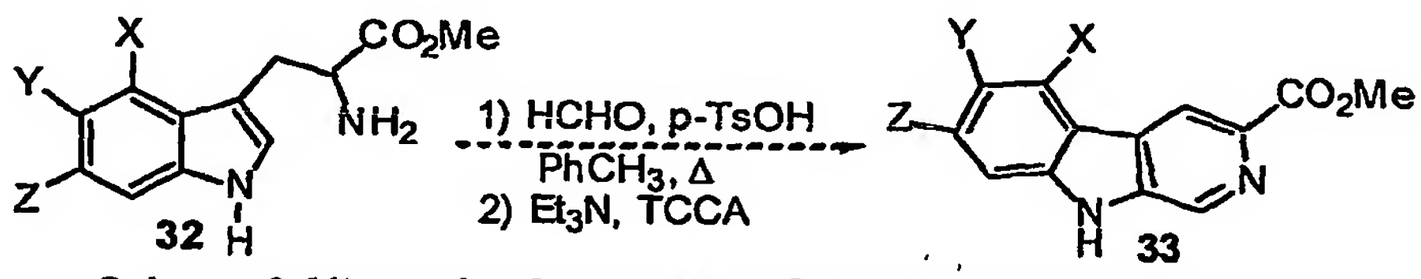
Scheme 7 Synthesis of C-5 and C-6 Substituted β-Carboline Derivatives

Figure 7



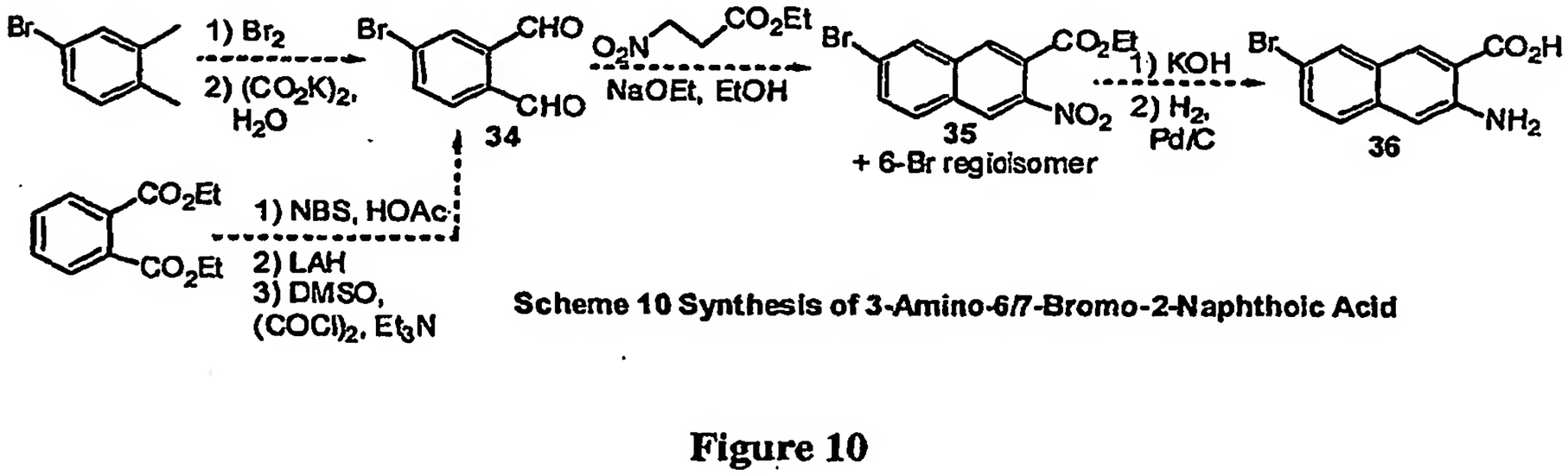
Scheme 8 Synthesis of C-3 Alkyl Substituted β-Carboline Derivatives

Figure 8



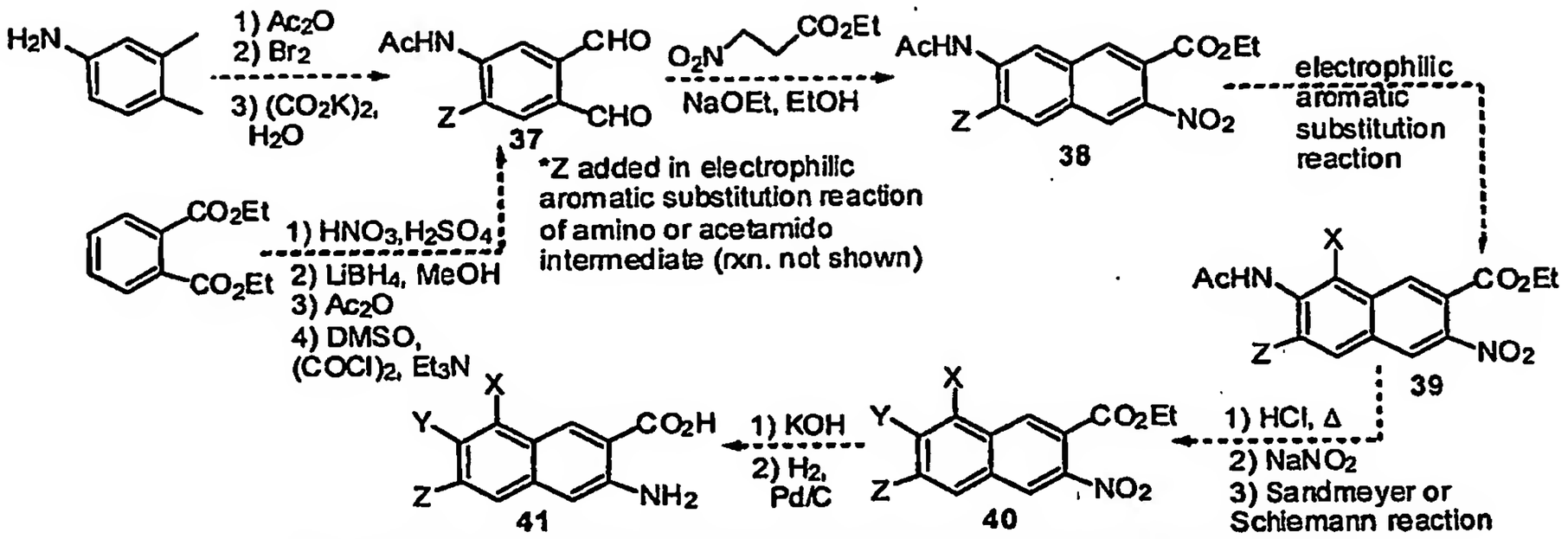
Scheme 9 Alternative Synthesis of β-Carboline Derivatives

Figure 9



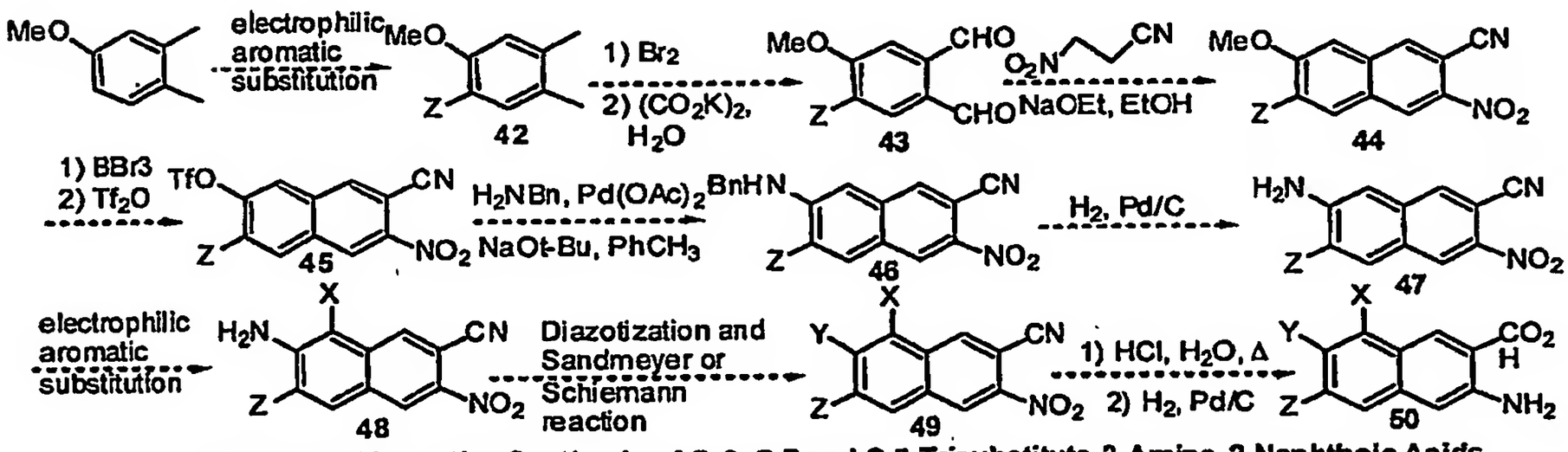
Scheme 10 Synthesis of 3-Amino-6/7-Bromo-2-Naphthoic Acid

Figure 10



Scheme 11 Synthesis of C-6, C-7 and C-8 Trisubstittued 3-Amino-2-Naphthoic Acids

Figure 11



Scheme 12 Alternative Synthesis of C-6, C-7 and C-8 Trisubstitute 3-Amino-2-Naphthoic Acids

Figure 12

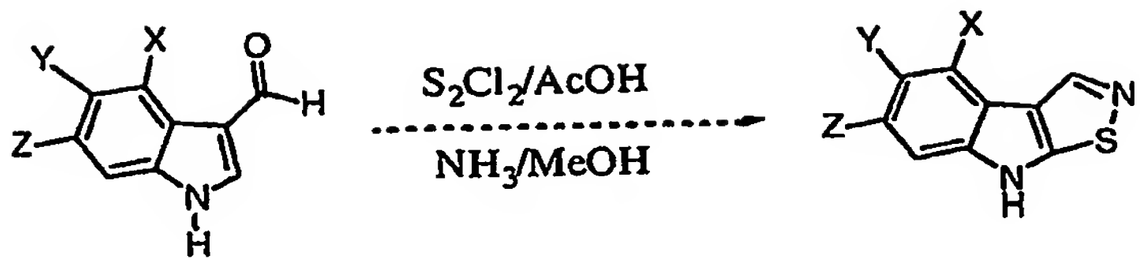


Figure 13

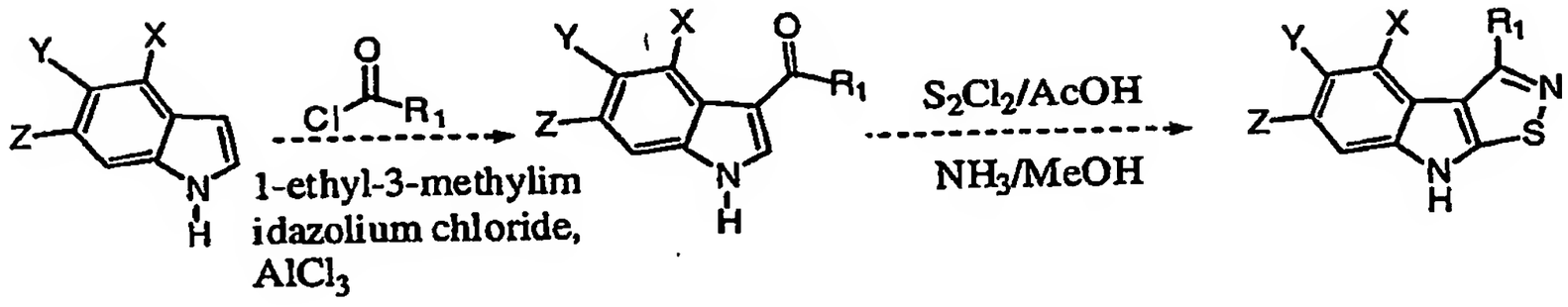


Figure 14

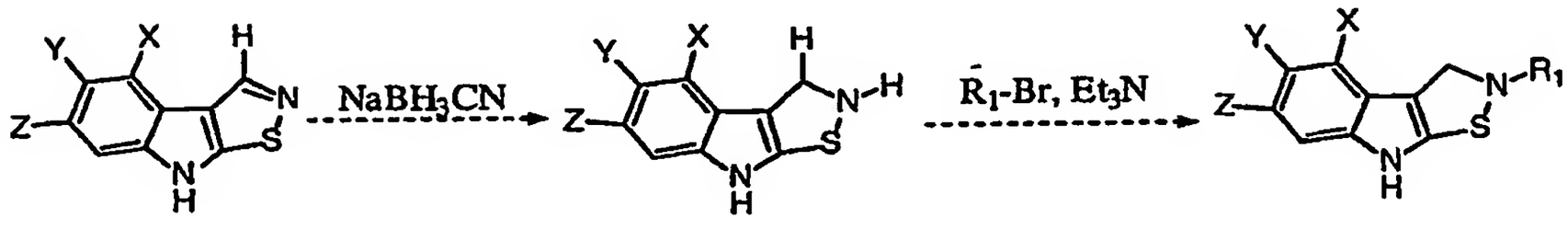


Figure 15

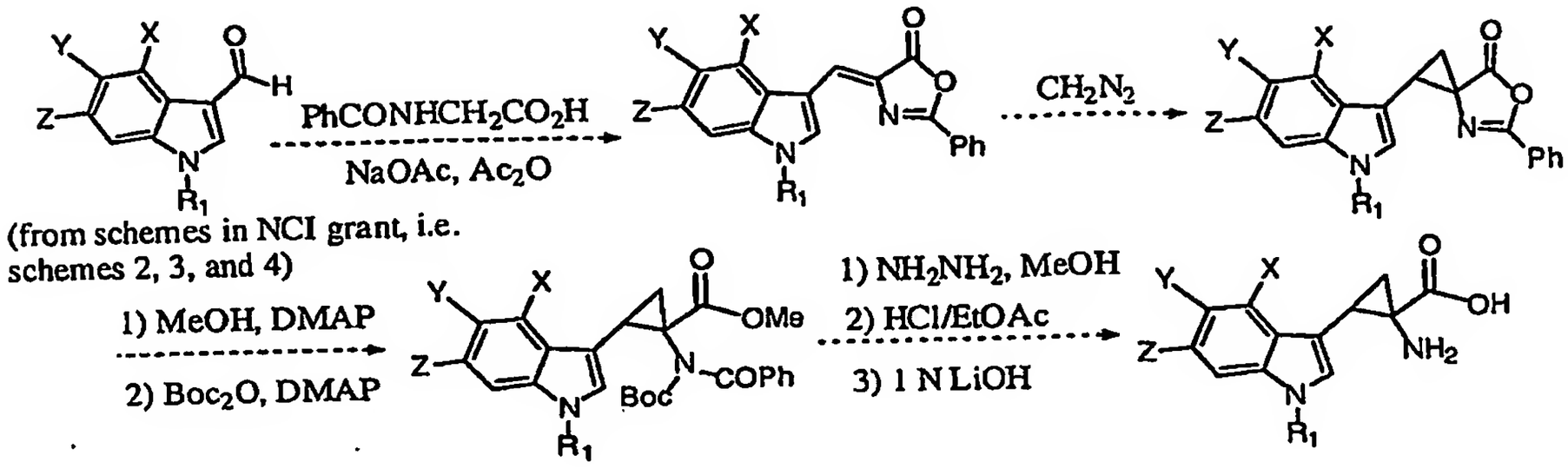


Figure 16

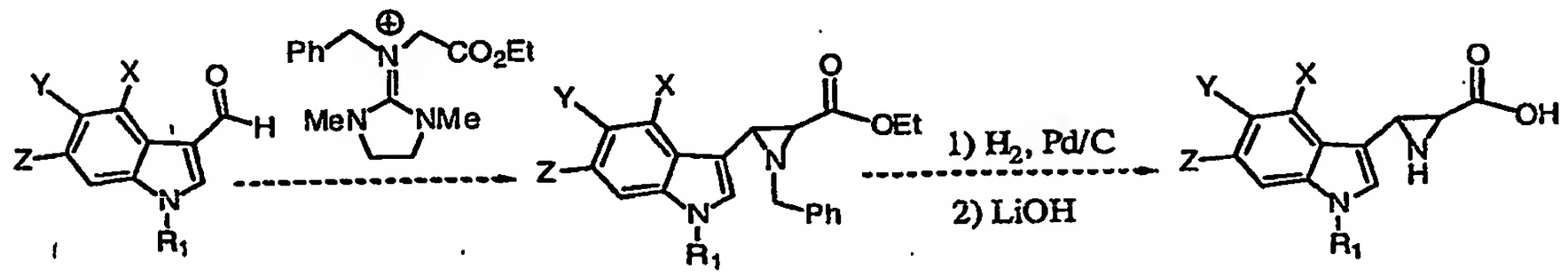


Figure 17

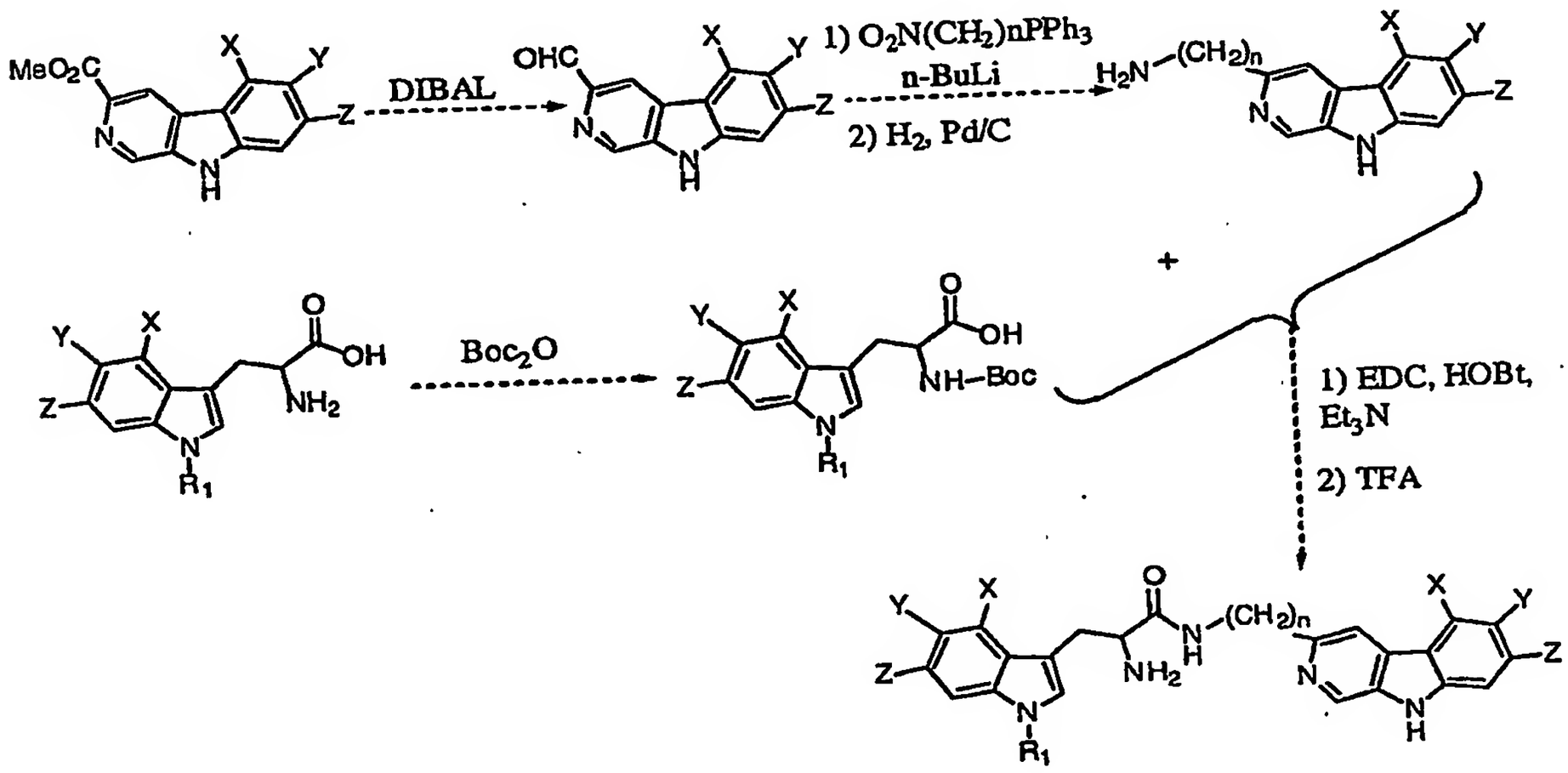


Figure 18

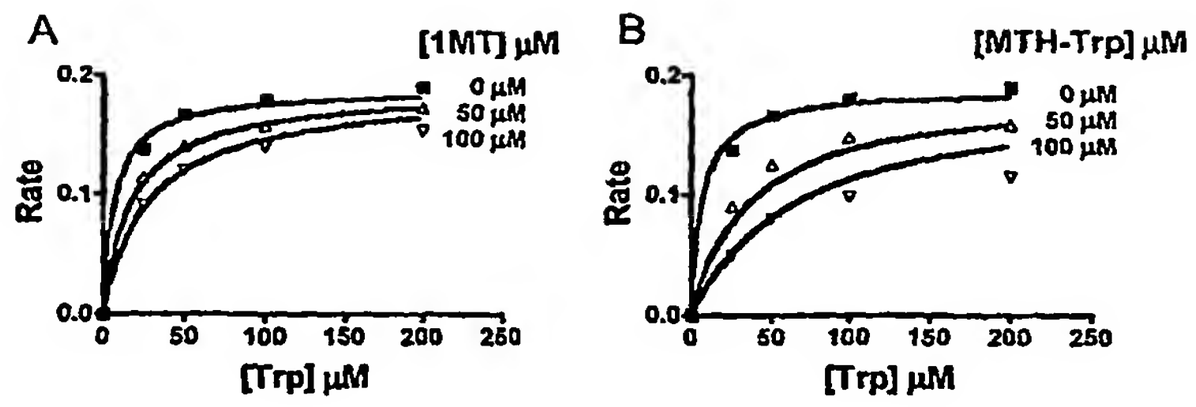
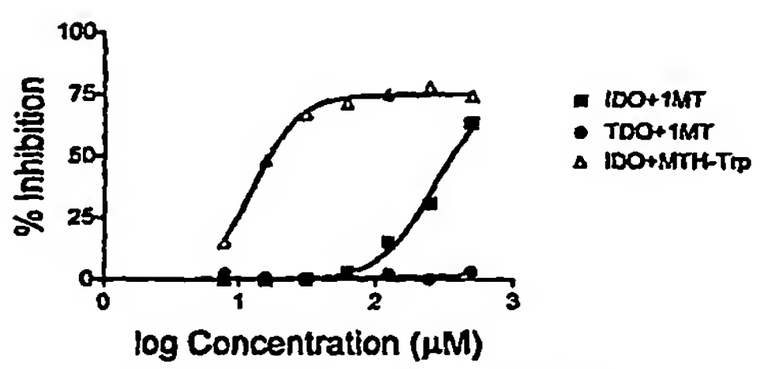


Figure 19



	IDO+1MT	IDO+MTH-Trp
HILLSLOPE	2.259	2.606
EC50	268.9	12.85

Figure 20

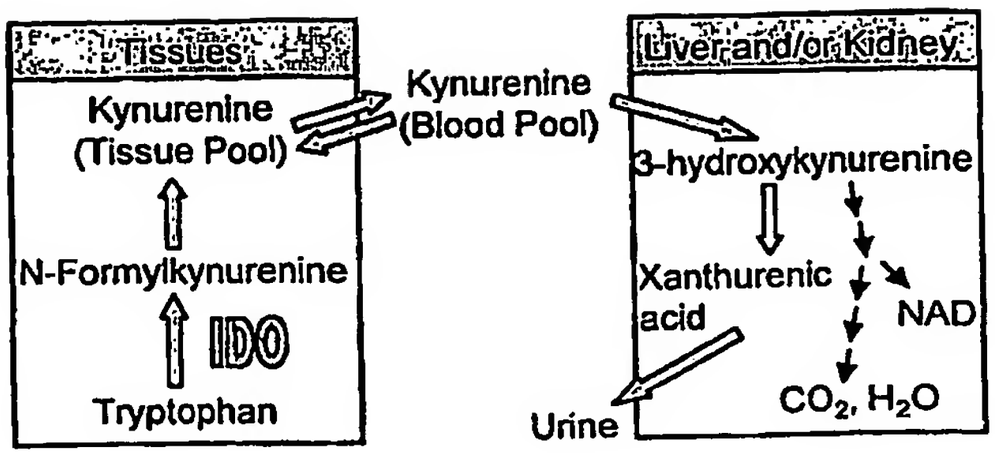


Figure 21

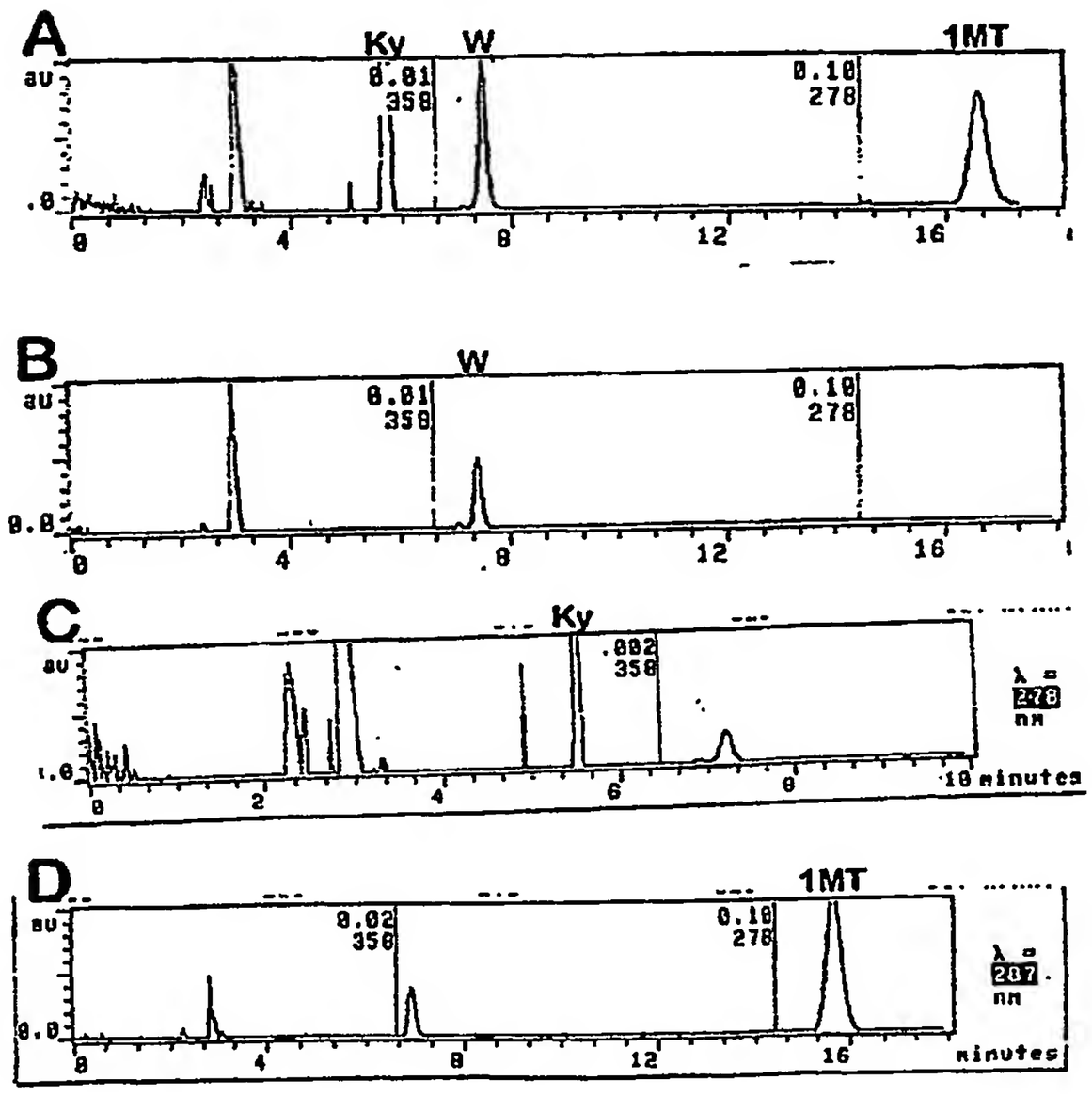


Figure 22

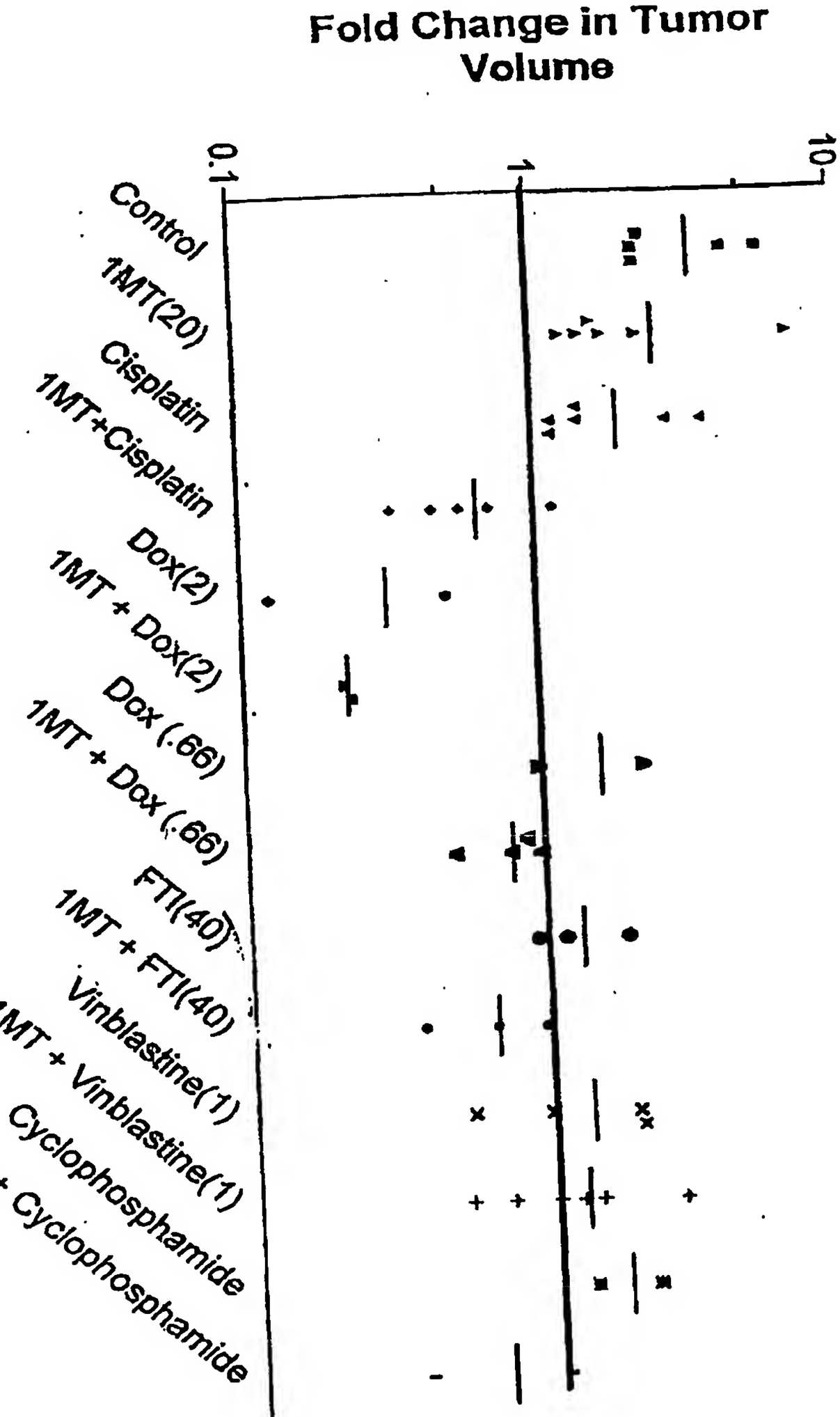

Fold Change in Tumor Volume
0.1
1
10
Control
1MT(20)
Cisplatin
1MT+Cisplatin
Dox(2)
1MT + Dox(2)
Dox (.66)
1MT + Dox (.66)
FTI(40)
1MT + FTI(40)
Vinblastine(1)
1MT + Vinblastine(1)
Cyclophosphamide
1MT + Cyclophosphamide

Figure 23